JOURNAL OF

The American Geriatrics Society

Volume IV *August 1956* Number 8

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Entered as second-class matter at the Post Office at Baltimore, Md. Subscription price $10.00 per volume. Published monthly.
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JOURNAL OF
The American Geriatrics Society

Official Journal of the American Geriatrics Society

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Subscriptions. The *Journal* is published monthly; twelve issues (Jan.–Dec.) constitute a volume. Subscriptions are sold on a volume basis, prorated if back volumes are not available. The subscription price is $10.00 per volume, plus $.75 per volume postage to foreign countries and the Postal Union, and $.25 per volume to Cañada. Subscriptions for members of the American Geriatrics Society are included in the annual dues which are $15.00. Single copies, when available, are $1.25 per copy, plus $.25 postage outside the United States. Publisher must be notified 60 days in advance of change of address. Undeliverable journals will be destroyed.

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JOURNAL OF THE
American Geriatrics Society
Official Journal of the
American Geriatrics Society · American Therapeutic Society · Texas Geriatrics Society

VOLUME IV *August, 1956* NUMBER 8

LIMITATIONS OF SUBJECTIVE SYMPTOMATOLOGY IN THE PREVENTION AND TREATMENT OF HEART DISEASE*

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INTRODUCTION

Subjective symptoms are the natural indicators of physiologic strain and pathologic disturbance. They are of great importance because they influence our behavior throughout life. Ideally, under conditions of increasing physiologic stress, they should make us increasingly aware of the strain being imposed; and, under conditions of pathologic disturbance, the character of the symptoms should parallel the gravity of the disease. That these ideals are not fully realized no one will deny. It is the purpose of this report to discuss the limitations of subjective symptomatology in persons who have or who are suspected of having heart disease.

THE PERCEPTION OF FEELINGS REFERABLE TO THE HEART

The heart is an extraordinarily insensitive organ. Most persons are rarely aware, and some are never aware of its beating. Scarring of the valves, the formation of atheromatous plaques, and even injury to the myocardium itself may take place without arousing any symptoms. Pain due to myocardial injury is experienced only when certain specific conditions have been fulfilled. Dyspnea and fatigue are secondary to changes in other organs; they are "symptoms once-removed." Palpitation is the only sensation which is easily and directly related to the heart (Fig. 1). A brief review of the mechanisms involved in the production of these symptoms will emphasize some of the difficulties encountered in their interpretation and in their practical application.

* Opinions or conclusions contained in this report are those of the authors. They are not to be construed as necessarily reflecting the view or endorsement of the Navy Department.

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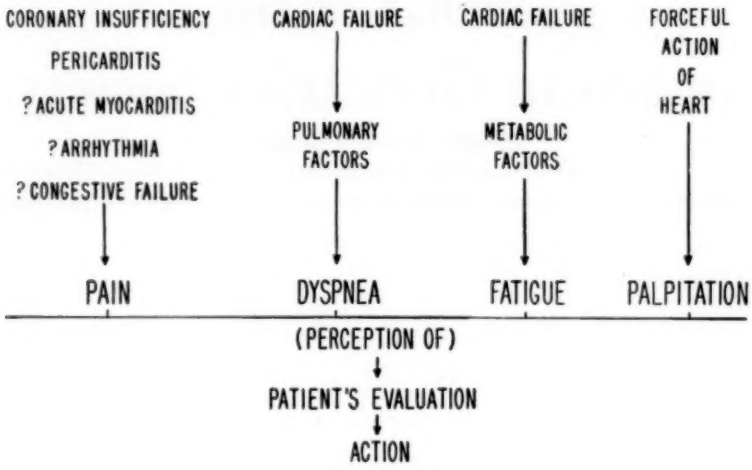

FIGURE 1

PAIN

The most frequent and the most important cause of pain referable to the heart is disease of the coronary arteries. However, not all patients with disease of the coronary arteries suffer pain. Even for those who do, it is a relatively brief experience. The pathologic changes in the coronary arteries may be present for many years, yet pain may be felt on few occasions and the total duration is mostly properly expressed in hours. The reason for this is to be found in the special circumstances which must obtain before pain is perceived. Only the main links in the chain of events will be reviewed here, partly because this is sufficient to illustrate the fact that many different pathophysiologic mechanisms are involved and partly because some of the mechanisms are either unknown or but poorly understood.

The sequence of events is summarized in Figure 2. It is generally agreed that the pain is causally related to coronary insufficiency, a pathophysiologic state wherein the blood supply is insufficient to meet the demands of the working heart. The events which precede coronary insufficiency fall into two main categories, namely, predisposing factors and precipitating factors (1). The former include such things as the narrowing of the coronary arteries as the result of atherosclerosis, valvular disease, the increase in muscle mass relative to the number of capillaries, and the amount of hemoglobin in the circulating blood. These factors may be present in considerable degree over long periods, yet not give rise to pain.

Some additional complication is usually required to trigger the pain-inciting mechanisms. These precipitating factors include such things as thrombus formation in a coronary artery, hemorrhage, hypoxia, exercise, and excitement. They are added of course to whatever predisposing factors may be present, and it is the combined effects which are the final determinant. If these factors are of a functional nature, they may readily be reversible, as in the case of an increase in work of the heart following exercise. On the other hand, thrombus formation

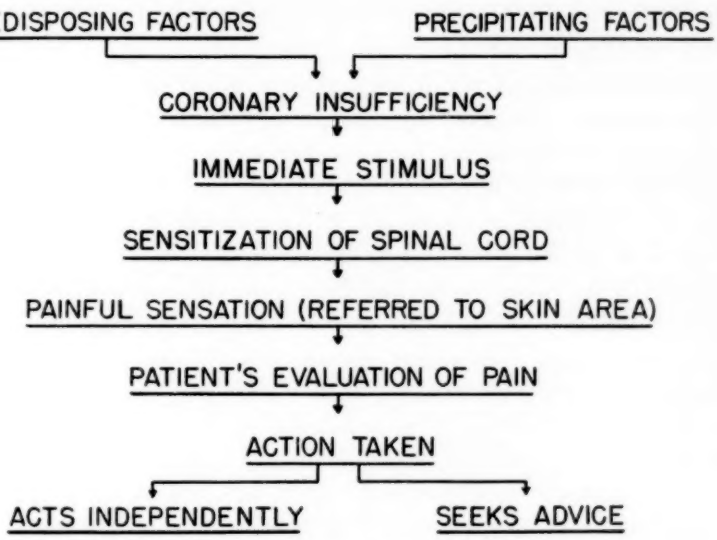

FIGURE 2

and myocardial infarction represent structural changes which are in large part irreversible. Consequently, coronary insufficiency will be present for a relatively long time.

There is still much to learn concerning the immediate stimulus to cardiac sympathetic nerve endings causing pain. We do not even know if the same stimulus causes pain in all instances of coronary insufficiency. There are strong reasons for believing that one stimulus at least is of a chemical nature, that it is a product of muscle metabolism, and that it is either a normal product which accumulates to abnormally high levels, or an abnormal product (2). There is evidence also that physical force incidental to pulling or stretching of nerves in the adventitia of the coronary arteries may be an effective stimulus (3).

It is difficult to explain the fact that under apparently similar conditions of coronary insufficiency, pain may or may not be felt. Whether or not this great difference is explicable at the stimulus level is unknown, but it must be regarded as one of the possibilities.

The afferent impulses which give rise to pain reach the spinal cord by way of the sympathetic system and the *rami communicantes* of the upper five thoracic nerve roots (4). This is probably the best understood link in the entire chain of events; what happens thereafter is far less clear and involves the mechanism of referred pain. That is to say, pain is not localized as coming from the heart but as coming from certain body surface areas. This "transfer" of the nerve impulse probably occurs in the spinal cord and, although there is evidence of some regularity in its distribution in that it may have a *radicular* or *metameric* projection, there is much variation among individuals and in the same individual from time to time.

It is necessary to point out that the sensing of pain is a psychologic phenomenon and is dependent on consciousness. Here, our knowledge of mechanisms is

so meager that we simply discuss pain as a phenomenon and attempt to measure its intensity and the thresholds of sensitivity (5).

From a consideration of the factors which incite the sensation of pain associated with coronary insufficiency, three important inferences may be drawn. First, there is an inevitable lag between the time of appearance of the precipitating factor and the time of perception of pain. The duration of this lag depends on the rate at which the precipitating factor influences unfavorably the balance between the work of the heart and its blood supply, to which must be added the time required for the stimulus to build up to suprathreshold levels. This period is frequently a matter of minutes but is sometimes longer. The lag may be shorter than one minute, but rarely shorter than fifteen seconds. The important clinical implication rests in the fact that within the lag period a patient may carry out activities which are injurious to him. For example, he would not be prevented from lifting a heavy object, running a short distance, climbing stairs with a load, or pushing an automobile stuck in sand or snow. These particular activities preceded the onset of infarction in many patients referred to our clinic. It has been postulated that strenuous effort may lead to rupture of a capillary in an atheromatous plaque, with subsequent thrombus formation (6). In addition to the risk of initiating infarction there is the risk of inciting arrhythmia of the heart and of injuring small areas of the myocardium marginally supplied with blood.

The second inference requiring comment concerns the reliability of the pain signal. That is to say, is pain regularly associated with the state of coronary insufficiency? Obviously it is not, because myocardial infarction may be painless and there is often electrocardiographic evidence of "injury" in the absence of pain. It is difficult to estimate the degree of reliability or lack of it, but in large series of cases of coronary heart disease angina pectoris is listed as a symptom in approximately 10 to 20 per cent.

Lastly, it is necessary to estimate the validity of chest pain as an indicator of coronary heart disease. Pain in the chest is an occasional occurrence in the life of everyone and, until properly qualified, is an unreliable symptom of coronary insufficiency. Important qualifications of the pain are concerned with 1) location and radiation, 2) character, 3) duration, and 4) the circumstance attending its onset, aggravation and cessation. If it is typical in these respects, the reliability of the pain as an indicator of myocardial ischemia is greatly enhanced. The reliability increases still further if additional qualifying factors are present, but falls off if some of these factors are atypical. Sometimes it is possible to make a correct diagnosis of coronary insufficiency on the basis of the pain alone, but at other times the diagnosis is in doubt unless corroborative findings complete the diagnostic pattern. Even with the help of every desired laboratory aid, diagnoses are missed. Today there is a tendency to err more frequently in ascribing chest pain to coronary insufficiency than in ascribing the pain of coronary insufficiency to other causes.

In discussing pain associated with coronary insufficiency we have chosen but one cause of heart pain and, probably, the easiest example in terms of our under-

standing of the mechanisms involved. It is also the best example in terms of reliability and validity. Nevertheless, it is clearly evident that the patient needs expert help in evaluating this symptom and in planning his behavior accordingly.

DYSPNEA

Dyspnea has been defined as an awareness of respiratory distress. Thus defined, it is strictly a subjective phenomenon; it is proper to say "the patient complained of dyspnea" but it is incorrect to state "the patient was observed to be dyspneic." There can be no objective equivalent to dyspnea, but the respirations may be described in terms of rate, depth, regularity, and associated phenomena.

The relationship between heart failure and dyspnea is summarized in Figure 3. Both forward and backward failure may induce congestive phenomena which in turn lead to stimulation of the respiratory centers through different pathophysiologic mechanisms (7). The sequence with the shortest time lag is backward failure of the left ventricle, pulmonary capillary hypertension, and stimulation of the vagal reflex to the respiratory centers. In the presence of left ventricular incompetence, any sudden increase in venous return to the heart, such as might occur on assuming the recumbent position, could cause an increase in pulmonary capillary pressure and reflex stimulation of the respiratory centers.

Pulmonary congestion interferes with the ventilatory movements of the

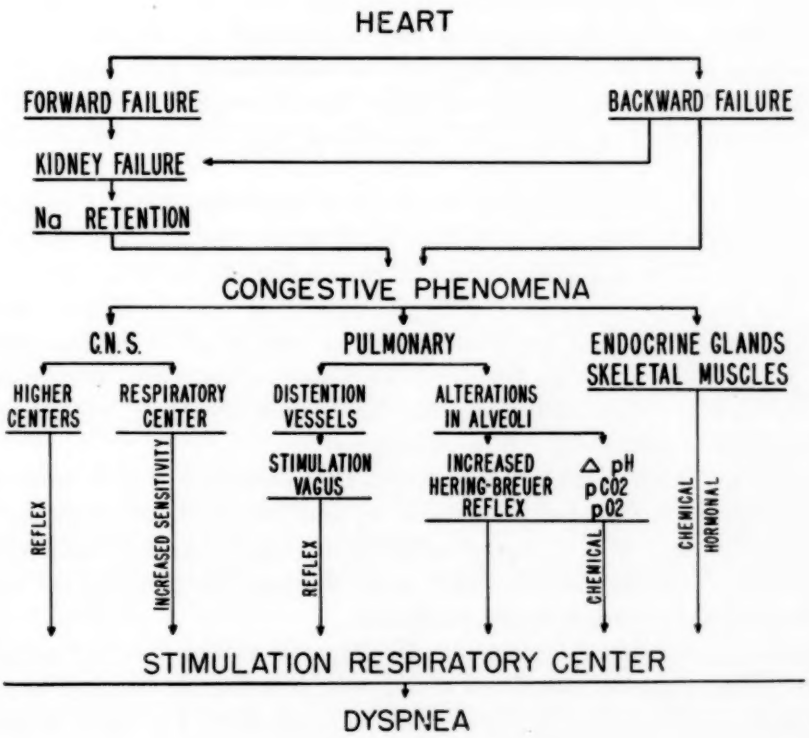

FIGURE 3

alveoli, causing hyperexcitability of the Hering-Bruer reflex and an increased rate of breathing. If pulmonary edema is present, there may be sufficient interference with the transport of the blood gases across the pulmonary membrane to affect the respiratory centers. These centers may also be affected by products of abnormal or disturbed metabolism of various bodily organs as a consequence of heart failure.

It is important to point out that the rate at which these pathologic changes occur is a significant variable. Thus, strenuous exercise, the onset of paroxysmal tachycardia, or the rapid administration of fluids intravenously causes marked displacements in bodily equilibria which may result in sudden and powerful stimulation of the respiratory centers. On the other hand, the gradual onset of heart failure with slow development of congestive phenomena can occur with little alteration in respiration.

The last link in our chain of events is dyspnea, and it is necessary to relate the objective phenomena of alterations in respiration to the feeling of respiratory distress, which is subjective. This has been expressed in many ways, but one of the most useful expressions is the following:

$$\text{Dyspnea} = \text{Sensitivity} \times \frac{\text{Ventilation (minute volume)}}{\text{Capacity to ventilate (maximum breathing capacity)}}$$

Sensitivity refers to the ease with which a person becomes aware of respiratory distress. There is much individual variation in the threshold for perceiving this feeling. Some persons complain of dyspnea when the alterations in respiration are slight; indeed, the degree of sensitivity may be regarded as abnormal, as in certain cases of neurocirculatory or neurorespiratory asthenia. At the other extreme are those who are remarkably insensitive and deny having dyspnea when, from objective evidence, it is determined that the ventilation has greatly increased.

Most persons do not complain of dyspnea until the ratio of ventilation to maximum breathing capacity is 0.30 to 0.35. When the ratio is 0.50, dyspnea is usually severe. This is a good means of measuring, objectively, the sensitivity factor. The presence or absence of hyperventilation may be determined objectively by measuring the oxygen-ventilation equivalent, *i.e.*, the amount of oxygen taken up from the air breathed. This may be expressed as the number of cubic centimeters taken from every liter of oxygen breathed, or the number of liters breathed in taking up 1 liter of oxygen.

Dyspnea is a fairly reliable symptom, as the conditions which led to dyspnea on one occasion are very likely to do so on another. Lack of reliability may be more apparent than real, and explicable by the fact that it is difficult to take into account all of the factors which cause dyspnea. In general, the reliability increases with increasing severity of disease.

Dyspnea is a nonspecific symptom. Healthy, as well as diseased persons have dyspnea. When a person *complains* of dyspnea, it is usually because he presently feels more limited by this symptom than in times past. The more dramatic the change, the greater the complaint. Few patients have the necessary knowledge

to be able to determine the factors which account for an increased susceptibility to dyspnea. Professional help is needed in relating the complaint of dyspnea to a particular cause. Once it has been established that this cause is heart failure, the dyspnea becomes a valid symptom of heart disease. There remains the difficult task of advising the patient what level of dyspnea should not be exceeded. To instruct a patient to stop work short of dyspnea may quickly lead to a further decrease in exercise tolerance based on activity. To encourage a patient to exercise to the point of considerable dyspnea may lead to cardiac strain and enlargement. In carrying out this evaluation in advising the patient, the physician must keep in mind qualitative and quantitative aspects of dyspnea in terms of reliability and validity. Dyspnea of effort is not a quantitatively reliable symptom during the initial period of work, because of the inherent delay in the chain of circumstances causing dyspnea and the ability of cardiac patients to incur oxygen debt. Dyspnea is a more reliable symptom when a steady state has been reached, and this should serve as the baseline. Changing values must be kept in mind with regard to both cardiac and non-cardiac factors. The latter include psychologic, physiologic, and pathologic elements.

FATIGUE

When the word fatigue is used in describing a complaint, it refers to the subjective aspects or the feelings of fatigue. In using this term we have in mind both the general feeling of weariness and the more specific feeling of weakness referable to any portion of the body.

Fatigue may be due to psychologic, physiologic, or pathologic factors. In patients with heart failure it may be difficult to determine how much of the fatigue is attributable directly or indirectly to heart failure. Even if a relationship is established between the two in a particular case, the problem remains of utilizing this symptom properly in the care and handling of the patient. At a certain level, fatigue becomes a compelling factor in causing a person to reduce his activity or to rest. However, a considerable degree of freedom exists prior to this point because cardiac patients as well as healthy persons can incur an oxygen debt. For a brief period of time they can call on the reserve store of energy in the muscles, which can be utilized anerobically. Thus, cardiac patients may carry out strenuous work for short periods without feeling fatigue. Patients with considerable reduction in cardiac reserve need professional advice regarding fatigue as a limiting symptom. It may be necessary to determine the patient's "fatigue profile" before worthwhile advice can be given. This refers to the diurnal variations and the influence of such constant factors as sleep, meals, the effect of stimulating drugs (*e.g.*, caffeine), and the effect of masking drugs (*e.g.*, alcohol).

PALPITATION

Palpitation may be defined as the subjective awareness of the beating of the heart. It is usually described in terms of rate, rhythm, and force of thrust. A healthy person may experience palpitation under different physiologic condi-

tions. There is much individual variability in the ease with which this symptom makes its appearance in consciousness. Predisposing factors are vasomotor instability and "sensitization" based on experience. Palpitation is also experienced in a variety of diseases and disorders.

Palpitation is a reliable symptom in that it is correctly related to the heart, but it is worth very little as a symptom denoting heart disease. It comes under the heading of an annoyance, and patients frequently attach more serious significance to it than it deserves. It is commonly related to a disturbance in rhythm which may be present in an otherwise healthy person.

SUBJECTIVE SYMPTOMATOLOGY OF HEART DISEASE FROM THE PATIENT'S POINT OF VIEW

Symptoms *per se* are worth very little from the standpoint of preventing primary heart disease. The obvious reason is that symptoms usually follow rather than precede the onset of disease. By the time the average patient complains of cardiac symptoms the heart is usually seriously affected and, in many instances, coronary insufficiency or congestive phenomena have appeared. It is an unfortunate fact that, insofar as heart disease is concerned, the individual receives little or no professional advice until failure or injury has occurred.

Most people err in believing that freedom from symptoms indicates the absence of heart disease. What it actually indicates is that the individual has sufficient cardiac reserve for the level of activities in which he engages. With increasing age many persons reduce their physical activities for a variety of reasons, none of which they ascribe to heart failure. Persons leading sedentary lives may never place a workload on the heart sufficient to disclose even a moderate degree of insufficiency. Hence, it is possible for them to have a considerable degree of heart disease in the absence of any cardiac complaints. This is exemplified by the many instances in which heart disease is discovered incidentally. On the other hand, persons engaged in strenuous activities are made aware of cardiac incompetence much earlier. Even then, these symptoms may be ascribed to "growing old," and the possibility that they are referable to the heart may not be considered. Thus the fact remains that many persons are unaware of the presence of cardiac disease.

The patient who knows he has heart disease is hopeful that he may get better and is fearful that he may get worse. The question is, how far can he rely on subjective symptoms in guiding and governing his activities. The answer cannot be given categorically, but a few generalities can be made.

It is only natural for the patient to be influenced by how he feels. If he feels well, it is difficult for him to believe that serious heart disease may be present. If he feels badly, he finds it difficult to believe that the symptoms may have no pathologic significance. In practically all cases, the patient with heart disease needs professional guidance. He usually needs to be told whether certain symptoms have their genesis in the heart or elsewhere. He needs to be told the significance of different symptoms, both from the qualitative and quantitative aspects.

The appearance and the severity of symptoms occasionally may provide the proper check on a patient's activity. However, this rarely is sufficient. It is necessary frequently for him to restrict his activities in the absence of naturally restraining symptoms, and it is necessary sometimes for him to disregard certain symptoms, at least insofar as their limiting influence is concerned.

These are educational problems and not all patients are apt pupils. It is not easy for the patient to distinguish between respiratory distress of functional origin and that due to heart disease. If he suffers from angina pectoris, he may wrongly regard other types of chest pain as being of cardiac origin. Many patients become forgetful and careless, especially in the absence of symptoms. Conversely, some patients need repeated reassurance, particularly if annoyed by symptoms which have little pathologic significance.

The imaginative patient with heart disease may live in fear of dying or of becoming greatly incapacitated. It is not remarkable that this affects his personality. In time he may begin to complain of symptoms which are not related to heart failure *per se*. In some instances these symptoms are appraised correctly, but not infrequently they are wrongly ascribed to heart failure. Some patients may become acutely aware of symptoms which are rightly ascribable to the heart but which have, through some mechanism of facilitation, become intolerable. This poses an even more difficult problem.

SUBJECTIVE SYMPTOMS OF HEART DISEASE FROM THE PHYSICIAN'S VIEWPOINT

The physician is interested mainly in diagnosis and treatment. Careful inquiry into the patient's subjective symptomatology is not only essential, but it may be the most valuable part of the medical examination. It is particularly essential in the diagnosis of functional disorders *per se* or when the recognition of a functional disorder is the only or chief clue to the underlying heart disease. The analysis of symptoms is dependent in part on the intelligence, keenness of observation and cooperation of the patient and in part on the ability of the physician. The very young, the very old, and the very ill patient cannot be as helpful as he might otherwise wish to be. Sometimes the patient does not wish to be helpful and tends to minimize or to exaggerate his symptoms, depending on whichever may be of advantage to him. Altogether, these constitute serious limitations in the over-all usefulness of the information obtained from the patient.

Physicians differ in effectiveness with respect to the analysis of cardiovascular complaints. This is not due so much to basic differences in ability as it is to differences in interests and in the amount of time devoted to history taking. This is not the place to elaborate on methodology; suffice it to say that a thorough understanding of the underlying pathophysiologic mechanisms and experience based on conscientious practice are two essentials.

It is important to emphasize that if there are discrepancies between the patient's complaints, the findings on physical examination, and the evidence from the laboratory, a thorough re-evaluation should be carried out. Errors in diagnosis are often traceable to inaccurate evaluation of the symptoms and complaints. The patient may find it hard to understand the physician's emphasis

on diagnosis until it is explained that there is little doubt as to the treatment of choice if an accurate and complete diagnosis is made.

Assuming that the physician has made an accurate evaluation of the patient's symptoms and recognizes their limitations, he still may have a problem in persuading the patient to follow a particular regimen, if it appears to the patient to be out of line with his symptoms. It is only natural for a patient to wish to do things which appear to be well within the limit of his capabilities. This is especially the case if the load on the heart is below the level at which any symptom is perceived. This accounts for the difficulty often experienced in restricting the activities of a patient following myocardial infarction.

The patient who is acutely aware of his symptoms may restrict himself unduly. It may be all but impossible to convince patients who are annoyed with ectopic beats that these are not the result of serious underlying heart disease. Inactivity quickly lowers exercise tolerance and even healthy persons, if sharply restricted in activity, experience severe symptoms on small exertions. The practicing physician assumes no responsibility until a person presents himself as a patient—a serious deficiency in the activities of the medical profession in caring for mankind. This comes under the heading of preventive medicine but, except in the field of industrial medicine, little is being done prophylactically at the doctor-patient level.

SUMMARY AND CONCLUSIONS

Subjective symptoms have serious limitations as indicators of heart disease and heart failure. Pathologic changes of considerable degree, carrying potentially serious consequences, may be present with relatively little reduction in cardiac reserve. Patients with heart disease and great reduction in reserve may not complain of symptoms at low levels of activity. Patients in whom cardiac symptoms develop at low levels of work during the "steady state" may still be capable of strenuous work for short periods. The absence of restraining symptoms in this period is due to the time lag in the long sequence of events which must precede the onset of symptoms due to coronary insufficiency and primary heart failure. This "overload" may be harmful. Conversely, patients may complain of symptoms which are out of proportion either to the gravity of the underlying disorder or the degree of heart failure or both. The most important symptoms of heart disease are nonspecific; hence, there is much opportunity for error in ascribing their genesis to a specific organ.

It is the natural thing for a person to be guided in his behavior by how he feels. In the absence of cardiac symptoms sufficient to arouse complaints, any measures taken to prevent the development of heart disease or its complications, or to treat existing heart disease and heart failure, must be based on knowledge obtained from other sources. It may be difficult for the patient properly to appreciate this apparent discrepancy between his state of health and the way he feels. Moreover, it is easy for the patient to become a cardiac "backslider." This is particularly the case when the evolutionary changes in the heart are slow, and long periods go by with little or no change in cardiac reserve. Long-range treatment requires frequent re-evaluations and frequently repeated instructions.

The patient who *complains* of symptoms referable to the heart adjusts his activities accordingly; yet these symptoms may not be accurate indicators of the presence of heart disease or of the degree of cardiac incompetence. In these instances it is often difficult to reassure the patient adequately and to prevent him from unduly restricting his activities.

The physician is handicapped as well as helped by the subjective aspects of cardiac symptomatology. He may have no opportunity to provide medical care until symptoms of severe heart disease cause the patient to seek medical aid. Even if the physician has the opportunity, he is faced with the difficult problem of planning a realistic regimen and the even more difficult problem of gaining wholehearted cooperation. Whatever the reasons, the fact remains that the physician in private practice devotes little time to the prevention of heart disease. The indoctrination of patients to the value of periodic examinations, regardless of the status of symptoms, will further this cause. The interest of the physician is aroused, however, if signs of heart disease are found, even though the patient has no complaints. He then may have a strong argument for instituting a medical regimen. To succeed in this, he must persuade the patient that he is not as well off as he feels. At what point the physician is justified in giving up further attempts at persuasion is hard to define. Both physician and patient have a responsibility here, and failure to implement a worthwhile regimen cannot be lightly charged to either.

The purpose of this report is to emphasize the limitations rather than the usefulness of subjective symptoms in the prevention, diagnosis, and treatment of heart disease. It has been shown that these symptoms are rarely the result of heart disease *per se* but rather of heart failure. Hence they are of no positive value in prevention, and of small value in the detection of the early stages of disease. Even when symptoms of heart failure have appeared, they cannot be relied upon under all circumstances. The limitations are both qualitative and quantitative. Qualitatively, the presence or absence of symptoms may carry the wrong implication. Quantitatively, the severity of symptoms may form a poor guide for the activities of life.

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NUTRITION AND THE GERIATRIC PATIENT*

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A year ago at this meeting my talk was concluded as follows: "It may be said in summary that sound nutrition in the elderly differs only slightly from that in the younger adult. The plan should include the following:

"1. Fewer calories. Because of the need of fewer calories, activity somewhat above the maintenance level should be encouraged. Such activity will also stimulate the peripheral circulation, strengthen bones, and improve gastrointestinal activity.

"2. A smaller proportion of calories contributed by fat and a larger proportion by protein. The protein should be selected to provide good nutritional quality at each meal, but this can also include cereal and vegetable proteins.

"3. Dietary modifications necessitated by poor dentures, low income, inadequate cooking facilities, and poor appetite.

"The first two of these recommendations would probably improve the health of the young adult and delay the onset of aging.

"The application of the findings of experimental nutrition to the health of man has great potentialities in many problems of medicine, both therapeutic and preventive. Today this is as important in the health problems of older persons as it was a generation ago in pediatrics, and the anticipated results can be equally important."

Now, a year later, it seems to me these same words still summarize the present relationship of nutrition to the geriatric patient.

Probably of more importance are the applications of nutrition to the prevention of physiologic aging. Two important health factors which unquestionably advance physiologic aging are obesity and atherosclerosis.

Our Department of Nutrition at Harvard conducts active research in both areas, and both problems are considered to be basically nutritional in their origin. I should like to tell you briefly about some of our recent findings in one of these fields, namely that of atherosclerosis. Most of what I shall relate is the work of several hardworking colleagues and graduate students, and not my own. Moreover, by telling only of our work, I do not mean to imply that others are not actively working on the nutritional factors in atherosclerosis. My time is limited, however, and it's easier to tell you about our own work; obviously we think it important or we would be doing something else.

Prior to this April 1955 most of our researches on atherosclerosis were under the direction of my colleague, Dr. George Mann. Since he left our Department they have been continued and extended largely by Drs. Hegsted, Portman and

* Presented at the Graduate Symposium on Geriatric Medicine, American Geriatrics Society, New York, N. Y., November 30 and December 1, 1955.

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Lawry. First I should like to tell you briefly about our data on the lipid levels of Guatamalan subjects subsisting largely upon vegetarian diets, a study which we conducted in cooperation with the Institute of Nutrition of Central America and Panama (1). These researches revealed an unexpected dissociation of the serum beta-lipoprotein and cholesterol levels. The subjects showed low and almost constant cholesterol levels at all adult ages. The levels (about 150 mg. per 100 ml.) for both sexes of that adult population, are characteristic of those for children in North America. In contrast, the serum beta-lipoprotein levels in the Central American subjects were similar to those of the North American subjects when compared according to age and sex. It became of interest to examine the hypotheses that some characteristic of the environment of the Guatamalans might account for these variations. There were two conspicuous differences between the study groups: 1) The Central Americans were found to eat much less fat than the North Americans. Although it has been shown that limitation of dietary fat will often lead to a reduction of the serum cholesterol and serum beta-lipoprotein levels, there has been no evidence that this treatment will selectively lower the level of cholesterol, leaving that of the beta-lipoprotein unchanged or increased—an hypothesis that would be necessary to explain the Central American findings. 2) The studies in Central America indicated that, although these subjects were thinner than age-matched and sex-matched North Americans, the Central Americans consumed more food daily in relation to body size. These facts could only mean that high energy expenditures by the rural Central Americans must account for the weight differences. This conclusion was consonant with the vigorous activity required of individuals in that agrarian culture. We were thus led to consider that there might be some favorable effects of muscular exercise upon the regulation of the serum lipids which would selectively keep the serum cholesterol at a low level.

Similar studies, with similar results, were carried out in Nigerians with the help of Dr. Bruce Nichols of the Federated Nigerian Medical Service (2).

Other studies we conducted on adult American males indicated that under certain conditions changes in weight affect the concentration of serum lipids (3). Thus, we showed that a period of weight loss in human subjects will result in a reduction of the levels of serum lipoproteins and cholesterol, *but only if these were initially elevated*. Conversely, we showed that a short period of rapid weight gain, even if accomplished on a low-fat, low-cholesterol diet, will increase both of these serum lipid components.

We recently completed a somewhat similar, but more elaborate study, to which a vigorous exercise component was added. Some of you have probably read about this study, as it was published in the September issue of the *New England Journal of Medicine* (4).

Four medical students were engaged to participate in an experiment of ten weeks' duration. The subjects were paid a good wage in addition to their food, and this was the principal initial motivation of 3 of the men. The fourth, although also paid, was interested in the experiment.

The men were fed at a research-diet table during the entire experiment. Food

was served by research dietitians, who measured the intake of food. The subjects were observed for the first week under these conditions, on an unrestricted food intake; they undertook their usual physical activity, and maintained their body weights at a nearly constant level. From the dietary measurements, the intakes of fat and total calories were computed and averaged for each subject. In the second period, which was of four weeks' duration, the caloric intake was approximately doubled while the fat intake was kept constant at the control level (about 175 Gm.). The subjects were required to maintain their body weights within 5 pounds of the mean weight during the control period by *strenuous* daily exercise. This was the period of high energy expenditure. In the third period, which was of three weeks' duration, the subjects returned to the control level of energy expenditure, but the high-calorie and constant-fat intake continued, thus permitting the deposition of body fat. In the fourth and final period, which was of two weeks' duration, the subjects were restricted in caloric intake, with the dietary fat again remaining constant. However, the exercise was omitted, except for that occasioned by their usual academic activity, as in the first and third periods.

The high energy expenditure was accomplished by a rigorous schedule of daily physical training. The subjects spent three hours every day engaged in vigorous physical exercise in a gymnasium. Swimming, basketball and sprinting proved the most useful activities; these were supplemented as necessary by cycling and outdoor running.

Blood was drawn in the post-absorptive state at weekly intervals during the experiment, and the serum was used for the measurement of cholesterol and of the beta-lipoproteins.

Three subjects completed the regimen in all details. The fourth subject was unable to maintain a constant weight and retired at the end of the second week of high energy expenditure. It may be of interest to mention that the subject leaving the experiment because of excessive weight gain was a tall, lean individual who initially argued that no one could make him gain weight.

In the 3 subjects who completed the study it became clearly evident that during the period of high energy expenditure, despite the large intake of calories, there was no essential change in weight, or in the levels of serum cholesterol or the lipoprotein fraction measured.

These observations indicated that the young men consuming high-fat diets were able to double their caloric supply without increasing the level of their serum lipids, so long as the excess energy was dissipated as exercise. The findings support the concept that serum lipid levels are related to the calorie balance of the body.

The experiment described may represent in a microcosm the nutritional progress of an adult American male. A period of high energy turnover in early adulthood may be followed by a long period of diminishing physical activity but with unchanging dietary habits. This leads in a variable time to an obese individual at middle age, with poor muscular development and elevated serum cholesterol and beta-lipoprotein levels, though without visible lipemia. More important, there is generally significant atherosclerosis in such a man.

After middle age, if this hypothesis be true, we have a patient in a state of advancing physiologic age, with atherosclerosis and its many unpleasant complications.

Next I should like to mention an interesting observation we made on the level of serum cholesterol following the intravenous administration of fat emulsions. Many of you know of our long-continued work on the preparation and study of fat emulsions that can be given by vein as a part of parenteral nutrition. For some years we have frequently observed that a few hours after the termination of an infusion of fat a transient hypolipemia may ensue. This hypolipemia not only involves the neutral fat but also the cholesterol and phospholipids of the serum. Some months ago my colleague, Dr. William Waddell, had occasion to cooperate with Dr. Walter Lever in a study of the disappearance of infused fat from the serum of patients ill with idiopathic hyperlipemia and primary hypercholesteremic xanthomatoses—diseases characterized by persistent elevation of the levels of certain blood lipids. Generally such patients are given a low-fat diet but, even so, levels of some of the blood lipids are markedly elevated, and atherosclerosis may be a common and early complication.

As was to be expected, infused fat in patients with idiopathic hyperlipemia was slow in leaving the blood stream, and the blood lipids took twelve to eighteen hours to return to pre-infusion levels. In patients without this disorder, the return took place within three to six hours following infusion of fat. Patients with idiopathic hyperlipemia generally have an elevated concentration of serum cholesterol, and much to our surprise this was rather markedly decreased following infusion of a fat emulsion. The decrease was evident by the termination of the infusion and became more striking as the neutral fat was cleared.

The following are a few specific examples. Four patients with primary hypercholesteremic xanthomatosis had an average serum cholesterol level of 556 mg. per 100 ml. prior to infusion of fat. Twenty hours after one infusion of fat, the average was 436 mg. per 100 ml. Nine patients with idiopathic hyperlipemia had a serum cholesterol level averaging 579 mg. per 100 ml. Twenty hours after a single infusion of fat emulsion, this average had decreased to 482 mg. per 100 ml.

Naturally, we were interested in seeing what would happen following several daily infusions of fat emulsion. A specific example will tell the story. A patient with idiopathic hyperlipemia and a serum cholesterol level that had for a long period consistently run above 600 mg. per 100 ml., was infused with fat for seven consecutive days. The following are the serum cholesterol values twenty hours after each of these seven infusions: 560, 475, 410, 370, 320, 300 and 260 mg. per 100 ml. Truly remarkable!

Those of you who are interested in knowing more about these observations should read Lever and Waddell's paper in the October issue of the *Journal of Investigative Dermatology* (5).

The fat emulsions that caused this decrease in the concentration of serum cholesterol contained 10 per cent cottonseed oil, 1 per cent soybean phosphatide and 0.3 per cent stabilizing agent; they were isotonic with glucose. We are now attempting, largely by means of animal studies, to find out: 1) which component of the fat emulsion mainly accounts for this marked lowering of the serum

cholesterol level, 2) what is the mechanism of the effects, and 3) whether it is applicable to the prevention of the induced hypercholesteremia involved in in experimental atherosclerosis.

That fat emulsions administered intravenously to man can result in a reduction of the serum cholesterol level is somewhat of a paradox, in view of other studies associating increased fat intakes with a high incidence of atherosclerosis. All of which goes to show that in research one never knows what may turn up.

CONCLUSION

The main problem in geriatric human nutrition is to improve nutrition before old age is reached, so that physiologic aging is delayed and the patient progresses in years in the best of nutritional health. This involves, among other things, the prevention or treatment of obesity and, most likely, the prevention and treatment of hypercholesteremia.

I should like to close with a few words taken in part from a letter I received a couple of months ago from Dr. C. Ward Crampton of New York, who wrote that physicians and others respond best to disability, disease, deficiency and distress. We must learn to respond equally well to prevention, protection, preservation, and the improvement of health, both personal and public. These are the principles which, if applied *prior* to advancing age, will make that period healthier and happier. Here, proper nutrition is of the most importance.

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DISCUSSION

Chairman McGavack: May we have questions at this time?

Dr. Daniels: I should like to ask Dr. Stare, who has presented a wonderful paper, what conclusions we can draw as to proper nutrition in old age.

I am glad that he stressed the prevention of old age because, like everything else, after old age is well upon us it is largely irreversible. How can we prevent the onset of old age? Do we have to start in the cradle, or with our grandfathers?

How can we improve nutrition so that we will not become doddering oldsters, but healthy, active and creative people in the prime of life? Can we do that? Do we know enough about it?

Also, will you be kind enough, if you can, to tell us the mechanism of reduction of hypercholesterolemia by intravenous fat. Is it advisable as therapy for those prone to have a high blood cholesterol concentration with atherosclerosis?

Do you believe that hypercholesterolemia and high fat are necessarily the cause, or one of the causes, or even a contributing factor in atherosclerosis?

Dr. Stare: Your first question was, What is good nutrition in the adult? I think the shortest way I can answer that is to say that in a recent issue of the journal of this society appears a paper I gave before this group almost a year ago. The question was discussed there in a little more detail. To summarize, I shall restate one or two points.

A reduction in calories is certainly important, actually beginning with infants. One of the unfortunate things in pediatric practice—and perhaps the pediatrician is spurred on by the opinion of the mothers of children—is the idea that the fatter a child, the healthier he will be. Many animal studies show this not to be the case. Therefore, a reduction in calories, probably from birth, is desirable.

The answer to the second point about better nutrition for the aged or for the adult, is a smaller proportion of calories contributed by fats and a larger proportion by protein. Protein derived from cereal and vegetables, when given with milk, is just as good as that from other sources.

I do not want to enter the controversy as to the value of vegetable and animal fats as compared with saturated and unsaturated fatty acids, because that is a subject under extensive investigation and the final answer is not known.

Your second question was whether or not the unusual and dramatic effect of intravenous fat in lowering serum cholesterol concentration approaches a therapeutic measure for such a condition. It certainly does not. I mentioned it because to me it is an exciting new finding. I can give one or two explanations, but I have not the least idea whether either is correct.

It has been known for years that fat which is infused, that is, neutral fat which is emulsified and introduced into the blood of animals and of man, is removed from the blood stream. In normal individuals, it is removed in three to six hours, but in individuals with a lipemic disturbance a longer time is required. As it is removed, it could conceivably carry with it the fat and cholesterol already present.

Using the same type of explanation—it is possible that the emulsifying agents in the fat emulsion may emulsify the cholesterol and carry it from the blood stream.

The last question was, Is it desirable to try to keep the level of blood cholesterol down, or to reduce it?

Again, many of the statements are a matter of opinion, but it is my belief that it is desirable. This attitude is based on firm experimental evidence, not in man but in animals, which can be summarized as follows: So far, experimental atherosclerosis has been produced in five species of animal—rabbit, rat, dog, chick and monkey—but only when an experiment could be carried out in which an elevated serum cholesterol level was induced and maintained for a certain length of time. That is the only way I know in which experimental atherosclerosis can be achieved. That is not the same as producing coronary heart disease.

I think Dr. Kinsell and others will be interested in an observation from our laboratory which has not as yet been published. For the first time we have observed in an experimental animal (rat) in which we produced a severe degree of atherosclerosis (found at postmortem), an extensive coronary thrombosis as well. To my knowledge, in the literature to date on experimental atherosclerosis, no one has commented on the production of thrombosis.

Dr. Kinsell: That was a beautiful paper, Dr. Stare.

I shall make this a leading question. Would you accept the thought that possibly the fact that you were using a highly unsaturated fat in your emulsion might have had something to do with the change in the cholesterol level?

We have carried out all our intravenous fat feeding with highly saturated fat, and have followed the serum concentrations of cholesterol, phospholipids, and other constituents.

In no instance have we seen any change in the serum cholesterol level, and we have used essentially the same emulsifier as yours.

Dr. Stare: Yes. I think that is a good lead. The cottonseed oil emulsions are obviously made with an unsaturated oil. You probably used emulsions of coconut oil, which is a saturated fat.

Dr. Kinsell: Hydrogenated coconut oil.

Dr. Stare: I think that is one of the possible explanations. There is no question but that the degree of unsaturation of fats consumed in meals, as well as in experimental studies, is an important aspect of this problem.

URINARY DIVERSION WITH VOLUNTARY CONTROL OF FECES AND URINE: REVISED OPERATIVE TECHNIQUE

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The title of this article is in itself a statement of a problem. In essence it involves diversion of the urinary stream while maintaining the following criteria:

1. Voluntary control of urination.
2. Voluntary control of defecation.
3. Complete separation of the urinary and fecal streams.
4. Prevention of reabsorption of urinary constituents.
5. A procedure which allows for removal of the primary pathologic lesion.

To illustrate, we may take a hypothetical case in which a pathologic condition of the bladder, let us say a resectable carcinoma, necessitates total cystectomy as the only hope for cure. To the genito-urinary surgeon the technical aspects of cystectomy are simple and the indications clear-cut. The problem of what is to be done with the urinary stream after cystectomy, however, is not simple or clear-cut, and it is this dilemma which has made genito-urinary surgeons appear so uncertain in approaching the subject.

As with many problems in surgery, the solution at one time appeared simple—namely, direct anastomosis of the ureters to the intestinal tract. The result was a continent patient who had both feces and urine under voluntary control of the intact rectum. It was after later studies by careful workers in the field that this solution became far less than perfect. A review by Creevy (1) showed that, exclusive of the primary pathologic lesion, the longer the patient survives with direct anastomosis to the gut, the more pronounced become the chances of serious complications in the form of chronic pyelonephritis from fecal contamination, hyperchloremia and acidosis from reabsorption of urinary constituents by the gut, and the subsequent failure of damaged kidneys to compensate for these conditions. Complete early surgery may cure the primary disease (bladder carcinoma), but diversion of the urine to the intact bowel frequently dooms the patient to death from another cause—renal failure and acidosis. Many attempts have been made to circumvent this chain of events, and the logic has been to separate the fecal and urinary streams completely. All such procedures have one common drawback—the patient is incontinent of feces or urine. For example, diversion to the skin is most incapacitating, as any practitioner who has had the misfortune of following these patients is fully aware. The leaking skin cups, cutaneous excoriation, clumsy leg bags—all these result in low morale, both for the patient and the doctor. Diversion of the urine to an isolated segment of ileum still involves an incontinent patient, who cannot pass urine under voluntary control and who has a urinary stoma on the abdominal wall. Diversion to the isolated rectum, as practiced by Boyce and Vest (2) and by Kinman and associates

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(3), is a good operation. It provides the patient with a sterile reservoir for urine (the rectal ampulla) under voluntary control in the lowermost segment of the colon, where it has been shown by Boyce that reabsorption of urine is at a minimum. Reflux of urine to higher segments of the colon is prevented because the rectal reservoir is isolated. An abdominal colostomy is used for the fecal stream. Whereas it is true that it is less difficult to control feces than urine on the abdominal wall, the result is still an incontinent patient.

Three attitudes have arisen from all these attempts:

1. To keep the patient comfortable by maintaining urinary and fecal volitional control, with cure of the primary lesion a secondary consideration, especially in the very aged.

2. An all-out attempt at primary cure (radical resection)—patient morale, productivity and after-care being secondary considerations.

3. A compromise approach, such as a scheme for incomplete separation of the fecal and urinary streams by establishing side pouches for the urinary stream (made of gut). There are also operations preserving the bladder neck and sphincter by anastomosing a segment of gut to the partially resected bladder.

No surgeon can be blamed for having any or all of the foregoing attitudes, depending on previous traumatic experience. It is to reconcile these divergent attitudes that the following procedure has been devised.

PRINCIPLE OF THE NEW OPERATION

This operation completely separates the urinary and fecal streams. It provides for continence and for voluntary control of both streams in the following manner:

The ureters are transplanted to the isolated rectal ampulla. The ampulla represents a closed sterile container or new bladder, with urination under control of the external sphincter ani and the intrinsic muscles of the anus.

By special dissection, the proximal sigmoid (the pathway for the fecal stream) is mobilized and drawn through a perineal area under the external sphincter ani, to open into the perineum immediately anterior to the anus. The external sphincter ani thus encircles both the anus (urinary outlet) and the perineal sigmoid stoma, hereafter referred to as the "new rectum."

The result is two separate openings, one for feces and one for urine, under the volitional control of one muscle. When the patient stands nude, there is no demonstrable abnormal opening on his body.

Total cystectomy or any surgical procedure on the primary lesion may either be undertaken at the time of diversion or reserved for a second stage.

The advantages of this situation are obvious from our initial discussion. To summarize, it provides all of the following:

1. Continence of feces, with voluntary control.
2. Continence of urine, with voluntary control.
3. Complete separation of fecal and urinary streams.
4. A sterile reservoir for containing the urine.
5. No regurgitation of urine to higher more absorptive segments of the colon.
6. Conditions that permit total cystectomy if necessary.

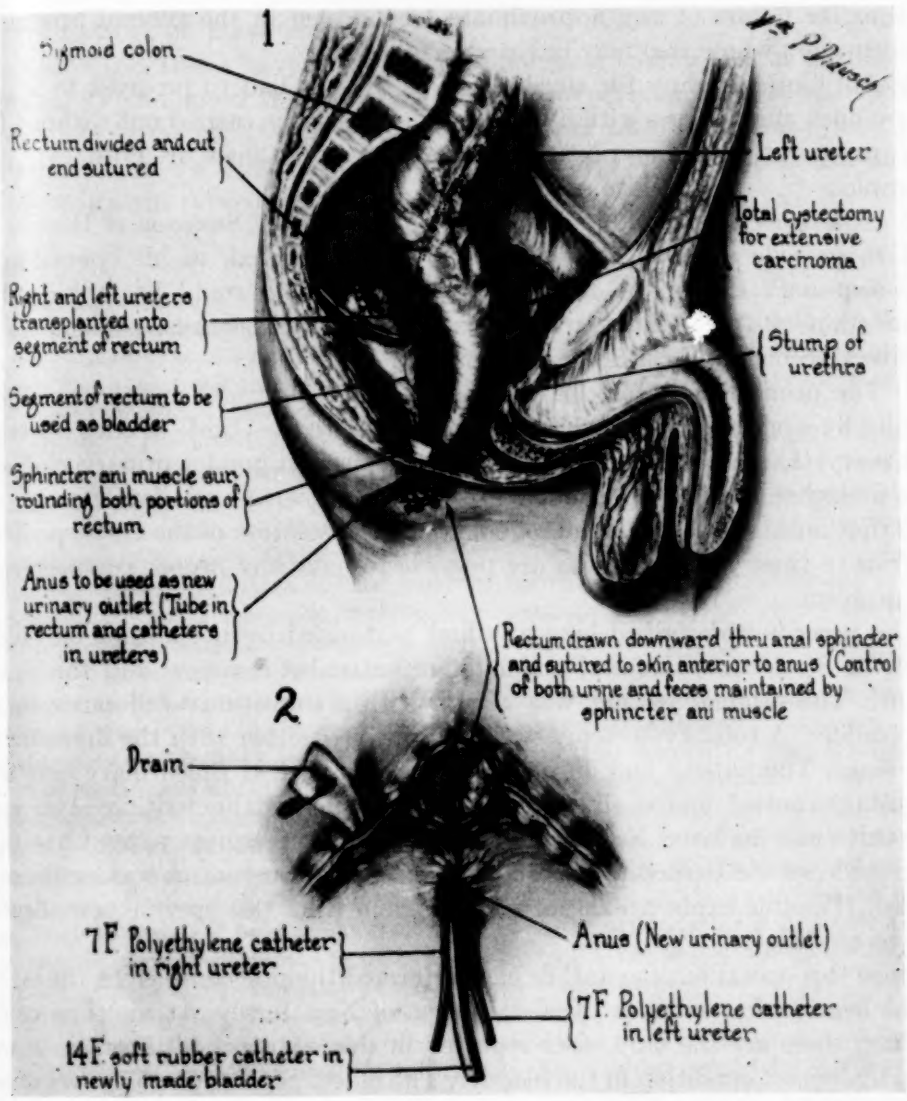
1
Sigmoid colon
Rectum divided and cut end sutured
Right and left ureters transplanted into segment of rectum
Segment of rectum to be used as bladder
Sphincter ani muscle surrounding both portions of rectum
Anus to be used as new urinary outlet (Tube in rectum and catheters in ureters)
Left ureter
Total cystectomy for extensive carcinoma
Stump of urethra
Rectum drawn downward thru anal sphincter and sutured to skin anterior to anus (Control of both urine and feces maintained by sphincter ani muscle
2
Drain
7F Polyethylene catheter in right ureter
14F soft rubber catheter in newly made bladder
Anus (New urinary outlet)
7F Polyethylene catheter in left ureter

FIG. 1. (**1**). Sagittal section illustrates the end-result of the procedure. Note that the fecal stream is anterior to, and completely separate from the sterile rectal bladder. The external sphincter ani is shown controlling both orifices. (**2**). The appearance of the perineum immediately after operation. (Reproduced by courtesy of the *Journal of the International College of Surgeons* from the article by Lowsley, Johnson and Rueda, reference 8.)

7. No abnormal orifice in an unnatural site of which the patient is conscious.
8. A distensible artificial bladder amenable to cystoscopic examination.

BACKGROUND OF OPERATION

The simplicity of this concept leads one to wonder why the operation had not been successfully accomplished before. Approximations (Levitsky) have been attempted in the past but were discontinued because of repeated failure. The

reasons for failure of any approximate scheme rest in the general progress of medicine as a whole, and may be listed as follows:

1. Antibiotic therapy for sterilization of the gut had to progress to a point where open anastomosis within the gut lumen could be carried out without fear. The preoperative gut sterilization technique, as outlined by Poth (4), is an example.

2. Experience in sigmoid mobilization, as reported by Swenson of Boston (5), had to precede a practical procedure. Swenson showed, in his operation for Hirschsprung's disease in children, that the sigmoid could be mobilized by transection of the sigmoid arteries without causing necrosis, as long as the collateral secondary arcades were preserved.

3. The prime reason for the procedure had to be established by a mass of studies by workers in the field. For example, before the efforts of such observers as Creevy (1) and Boyce (2, 6, 7), who demonstrated greater urinary reabsorption in higher colonic segments, there was no known reason for opposing the idea that anastomosis to the intact colon was the solution of the entire problem.

Prior to these studies, it was not possible to have any proper perspective on the problem.

The procedure described here was first performed by the author on July 3, 1953, at St. Clare's Hospital and later reported by Lowsley[1] and the author (8–10). The original patient was a man with a transitional-cell carcinoma of the bladder. A total cystectomy was performed, together with the diversion, in one stage. The patient had an uneventful recovery, had full urinary and fecal voluntary control, and is alive and well at the time of this writing—two years and three months later. Neither in him nor in any subsequent patient has there been evidence of contracture or obstruction of the new rectum, as was legitimately feared. (Possible explanations for such freedom from this specific complication will be made later.)

Since this operation, the author has performed the procedure eight times, and it has been performed once by F. R. Begen of New Jersey. At the time of this writing, these are the only cases reported in this country. All operations were for a malignant condition in the bladder. The oldest patient was 65 years of age, and the youngest was 20 months. Although bladder malignancy is not the prime indication (the operation is ideal for benign conditions of the bladder requiring diversion, such as Hunner's ulcer and exstrophy), malignant conditions provided enough experience with the procedure to prove its success. At present there are 6 living patients who have excellent functional results.

The original technique was worked out by study on cadavers. Although there is considerable divergence from previous techniques, as in any new procedure, no surgical principles are violated and physiologic principles are rigidly adhered to.

Consistent success depends upon some degree of cooperation by the patient, especially in the matter of not interfering with indwelling catheters and drains for the first few days. It is for this reason that attempts on dogs would probably

[1] Deceased.

be doomed to failure. Therefore, after the cadaver studies, the author went directly to work on humans.

Some complications have resulted from changing techniques for purposes of added safety and speed. The last case was a liomyosarcoma of the bladder in a 20-months old infant; the diversion operation and total cystectomy took four and a half hours—a length of time which compares favorably with that of any major abdominal procedure.

REVISED TECHNIQUE

A doubled rectal tube is inserted into the rectum and fixed to the skin by a suture. This provides for decompression of the new bladder and serves as an anchor for the intubating ureteral catheters. It also releases sigmoid contents if neomycin solution be used preoperatively. The end of the tube must be directed so that the ureteral catheters may pass unimpeded through its lumen.

A transverse lower abdominal incision is made. The peritoneum is quickly located in either the left or right lower quadrant, and opened. The incision is extended from angle to angle. The epigastric vessels are severed and ligated. No time should be wasted in the initial incision, as the procedure has many steps—some very exacting—and to consume time unnecessarily is detrimental to the patient.

The intestines are retracted upward, exposing the sigmoid, urinary bladder and parietal peritoneum. An incision is made in the parietal peritoneum over the brim of the pelvis. Both ureters are isolated and transected. Care is taken not to crush the proximal ureteral ends. A No. 00 atraumatic chromic catgut suture is placed in each proximal ureter, and the ureters are intubated with 7F polyethylene catheters. For purposes of identification, a white catheter is used in the right ureter, a blue catheter in the left.

With the urine draining off the field, attention is then directed to the rectosigmoid. Anastomosis is made where the ureters can enter easily without tension.

At this point the mesentery of the rectosigmoid is dissected to permit use of a Von Petz clamp. The operator makes sure the doubled rectal tube is out of the field (this is the reason for doubling the tube) and the clamp is closed on the bowel. No. 00 atraumatic catgut traction sutures are placed on each lateral bowel surface, above and below the double row of clips. With an assistant holding the traction sutures, the rectosigmoid is transected below both rows of clips. This insures that there will be no leakage of bowel contents from the proximal sigmoid as the dissection of the sigmoid attachments proceeds.

The rectal ampulla is now open. Arterial "spurters" will be noted and are a welcome sign of adequate circulation. If neomycin solution is used preoperatively, suction must be employed to prevent spilling over the peritoneum. The doubled rectal tube is grasped and straightened, and the excess tubing is excised. A heavy fixation suture is placed through the end of the rectal tube, and the tube is allowed temporarily to retract back into the rectal ampulla. This suture will be used to fix in place the ureteral intubating catheters.

A site for anastomosis is selected on the posterior aspect of the rectal pouch. Anastomosis is best accomplished on the posterior wall, as the ureters will then lie flat against the posterior curve of the pelvis, preventing looping or bowing of the ureters. Although this complication has not occurred, intestine could conceivably form a hernia through such a loop. A sharp-nosed clamp is then pushed from inside the rectal lumen through the wall at the selected site. The ureteral intubating catheter is removed from the ureter, and the No. 00 chromic catgut suture in the end of the ureter placed in the jaws of the clamp. The ureter is then pulled inside the rectal lumen. Working under direct vision from inside the rectal lumen, a direct mucosa-to-mucosa anastomosis is accomplished. Since the gut has been effectively sterilized by careful preoperative preparation (neomycin and Sulfathaladine, as outlined by Poth (4)), emphasis is best placed on a good anastomosis under direct vision, without fear of fecal contamination. This emphasis is in direct contradistinc-

tion to prior methods of anastomosis, in which fear of opening the bowel predominates over a more realistic concern for the long-term prognosis. Direct mucosal anastomosis under vision offers less chance of ultimate stricture formation, especially when the urinary reservoir is sterile. Intubating ureteral catheters are placed in the ureters. The rectal tube is elevated by the traction suture and the ureteral catheters are passed into the open end of the tube to the outside. This is why the position of the rectal tube when it is first introduced below is most important, for unimpeded passage of ureteral catheters is essential. The ureteral catheters are passed to the kidney pelves, but not too far, as pressure will cause bowing, making the ureteral loops previously mentioned. When the operator is satisfied the ureters lie flat against the curve of the pelvis, the intubating ureteral catheters are tied to the end of the rectal tube by the original fixation suture. This procedure insures that the intubating catheters will remain exactly in position and that the new rectal bladder will be decompressed by the indwelling rectal tube firmly fixed in place by a skin suture. There need be no fixation sutures between the serosal layers of bowel and ureters; such sutures are not only superfluous, but can cause kinking at the site of anastomosis, especially with normal distention of the new rectal bladder.

The rectal bladder is then closed in a double layer.

Dissection is now started on the proximal sigmoid. Branches of the sigmoid artery are ligated, leaving secondary arcades to provide adequate collateral circulation to the end of the bowel. After this, peritoneal reflections from the sigmoid to the left lateral wall are easily separated. The operator then determines when enough sigmoid is liberated to go through the rectovesical pouch and out through the perineum. There is no fixed rule for this, as the depth of the pouch varies. It is better to free an excess rather than find that more dissection is required with the patient in the perineal position. The best practice is to free what is thought to be an adequate length, then dissect free one or two more blood vessels. If the sigmoid needs more length during the perineal stage, the assistant can easily transect these vessels.

At this stage a cystectomy may be performed if indicated.

With the abdomen still open, the patient is put in the perineal position. A curved incision is made directly anterior to the anus, and the dissection is carried under the external sphincter ani to the rectovesical pouch. The peritoneum is opened and the opening widened by finger dissection, sometimes with the aid of the assistant. The assistant places one hand over the new bladder to protect it from injury and the operator passes curved uterine packing forceps from below up. The sigmoid traction sutures between the rows of Von Petz clips, together with a Penrose drain, are placed in the jaws of the forceps and the sigmoid is drawn into the perineum.

When the double row of clips is excised, the degree of bleeding will demonstrate the adequacy of the circulation to the bowel. The sigmoid is fixed by direct mucosa-to-skin sutures, insuring a good cosmetic result with this "new rectum."

The perineal wound is closed, leaving the Penrose drain protruding from one angle. The patient is returned to his original position and the abdominal incision is closed. Drainage above is advised.

POSTOPERATIVE CARE

As with any major surgical procedure, the usual measures are taken regarding antibiotics and fluid balance. Abdominal drains are shortened and removed first. The rectal tube and intubating catheters are removed in seven days. It is probably wise to leave the perineal Penrose drain in until after the intubating catheters are removed. This drains the site of the anastomoses and insures outlet of urine if a leak should ensue.

A non-residue diet is first given, followed by a soft diet. The stool is kept soft with mineral oil.

The earliest sign indicating the patient has control of his feces in his consciousness of passing flatus through the new rectum.

Rectal control usually comes after urinary control. It is generally established within two weeks if the stool is formed. Advice is given to the patient about practicing voluntary control of the feces.

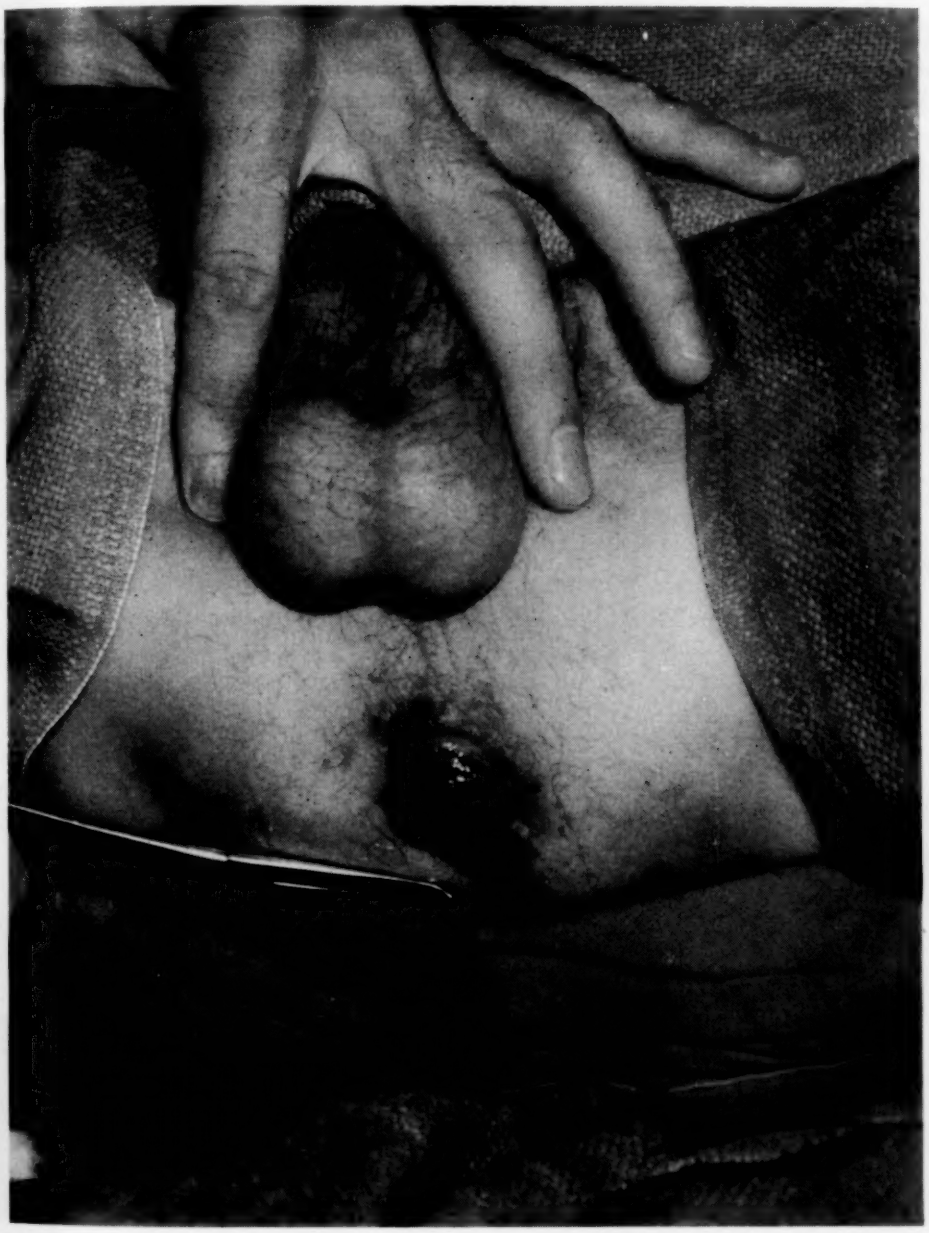

FIG. 2. Photograph of perineum in original patient one month after operation. Note the redundancy of mucosa in the new rectum. The location of the anus (urinary outlet) posterior to the new rectum is indicated by the clamp.

Temperature curves in these patients indicate no more prolonged sepsis or stress than with the average major procedure.

FUNCTIONAL RESULTS

The most gratifying aspect of this operation has been the results observed upon follow-up of the patients. They wear no appliances (Fig. 2); they are able to carry on normal work and social relations. Morale is high, as none is conscious of any demonstrable abnormal opening. The new rectum can only be seen when the patient bends from the hips (Fig. 3). Palpation of the new rectum induces the same sensation as palpation of a normal rectum, and the patient can constrict the external sphincter ani around the examining finger at will. There is no loss

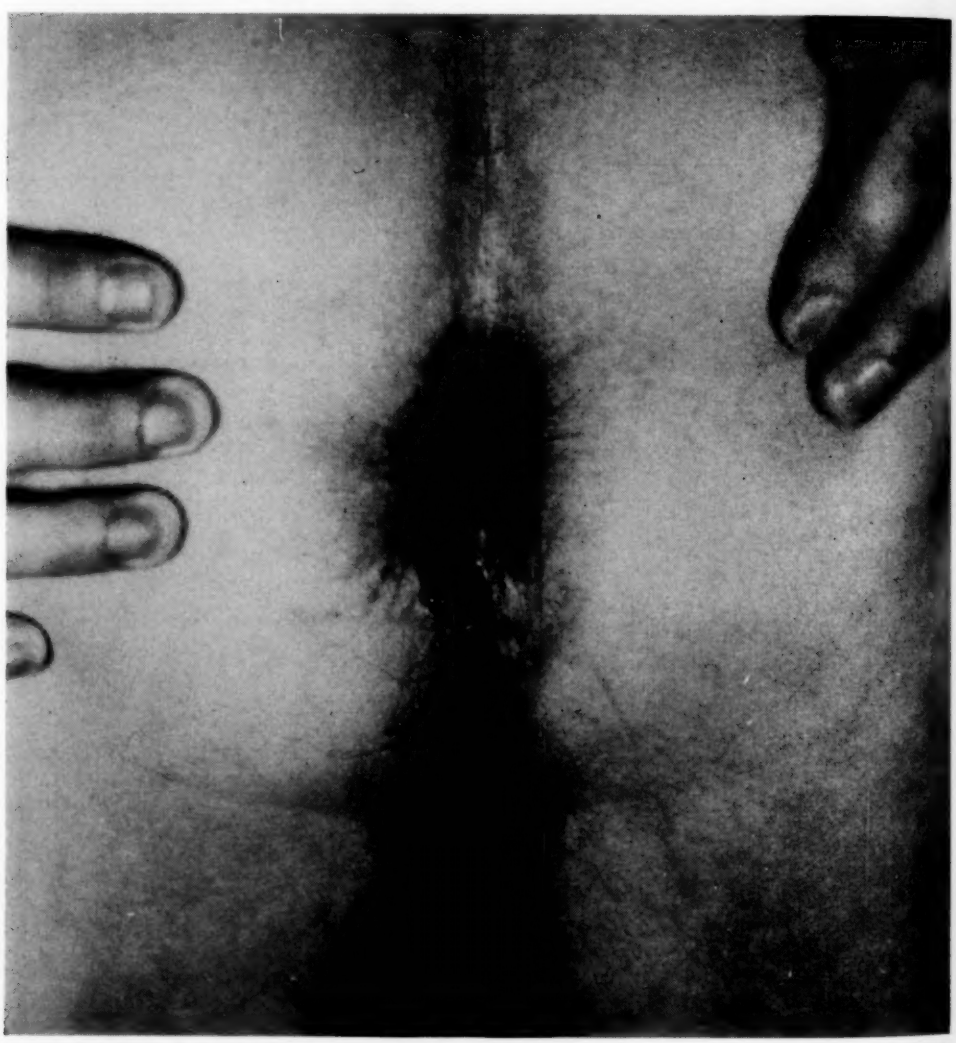

FIG. 3. Improved cosmetic result in a later case. Patient is bending from the hips, and the buttocks are spread to expose the new rectum and anus. Note lack of redundant tissue in the new rectum, compared with Figure 2. New orifice is completely invisible in this patient unless buttocks are separated.

of feces or urine on standing, walking or working. Stools are best kept formed, but soft. Some patients prefer to take a rectal flush in the morning to guard against constipated stool; this suffices until the next morning. Stricture of the new rectum—a complication originally feared—has not occurred in over two years. A possible explanation for this satisfactory result may lie in the nature of the external sphincter of the anus. The sigmoid is not encircled by parallel longitudinal fibers, as is the intestinal segment in an abdominal colostomy. It is encircled by muscle, circular in nature, the function of which is voluntary control of bowel contents. Thus, there may be no tendency toward stricture in the new rectum, just as there is no tendency toward stricture in the normal sphincter muscle of the anus.

A remarkable feature in some patients is the ability to hold urine while passing feces. The answer to this may lie in the action of additional intrinsic muscles of the anus.

Aside from patient morale, prognosis is excellent if the initial lesion is either benign or, if malignant, completely eliminated. Blood chemical elements remain at normal levels. If ureteral reflux does occur (it may be expected with normally high rectal pressure), it does not have the grave prognosis associated with reflux of contaminated urine.

SUMMARY AND CONCLUSIONS

The rationale of a new operation for diversion of urine with voluntary control of both feces and urine has been outlined, and a revised operative technique described. Follow-up observations have shown uniformly good functional results. Moreover, the possibility has been opened up of applying this procedure in conditions in which the patient has previously undergone simple ureterosigmoidostomy or operation for rectal bladder with colostomy.

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THE ENDOCRINE TREATMENT OF CLIMACTERIC (STEROID-DEFICIENCY) OSTEOPOROSIS

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The incidence of osteoporosis in the aged is unknown, but mounting evidence suggests that it is much more prevalent than has been realized. Not only is it often asymptomatic, but the diagnosis may be overlooked by the roentgenologist when density changes in the spine are slight. The recent report of Gershon-Cohen *et al.* (1) describing asymptomatic and unrecognized vertebral fractures in the osteoporotic spines of the aged is interesting in this connection. Despite the classic observations of Albright and Reifenstein (2) that menopausal osteoporosis is primarily a disorder of the bony matrix and that the decalcification is secondary, and despite their demonstration of the beneficial effects of estrogen and androgen, most physicians are apparently unaware of the therapeutic improvements which result from the administration of these hormones. Recently Spencer *et al.* (3), employing a calcium tolerance test devised by Schilling and Laszlo (4), showed that patients with osteoporosis excreted a larger proportion of intravenously administered calcium than did normal individuals—once again proving the futility of treating this metabolic disorder with calcium.

If osteoporosis be due to a steroid-hormone deficiency, why is it apparent in only certain postclimacteric patients, and why does it take so long to develop? What is the optimal therapeutic dose of estrogen and androgen, and why does clinical relief from pain occur so rapidly, whereas x-ray improvement takes many years? It was with the hope of answering these questions that the present study was undertaken.

CLINICAL MATERIAL

This report includes 62 climacteric patients (50 women and 12 men) with unequivocal x-ray evidence of moderate to severe osteoporosis of the spine; 6 control subjects (3 women and 3 men between the ages of 25 and 35 who were physically normal); and 3 postmenopausal women who had amenorrhea of five to ten years' duration but no clinical or x-ray evidence of osteoporosis.

The distribution of the 62 patients with osteoporosis of the spine is shown in Table 1. These data confirm earlier reports of increased frequency of osteoporosis in women, and also suggest that it appears earlier in women than in men. Compression fractures were seen in only 2 men (one was 55 and the other was 68 years of age) and in 14 women (5 were between the ages of 50 and 60, and 9 were over 60). If the incidence of compression fracture of the vertebral bodies is any

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TABLE 1. *Distribution of 62 Climacteric Patients with Osteoporosis of the Spine*

Women				Men	
Age	Number	Years amenorrheic	Number	Age	Number
35–40	3	under 10	2	45–50	2
41–50	12	10–15	12	51–60	4
51–60	31	16–20	18	over 60	6
over 60	4	over 20	18		

measure of the degree of osteoporosis, it would seem that osteoporosis is generally more severe in females than in males.

METHODS

Causes of decalcification other than steroid deficiency—such as inadequate dietary protein, vitamins and calcium, gastric anacidity and fatty stools—were systematically excluded.

Routine determinations included a complete blood count, urinalysis, fasting blood sugar and serum cholesterol levels, 24-hour thyroidal I^{131} uptake, and 24-hour urinary titers of estrogens, gonadotropins, 17-ketosteroids and corticoids. In all instances the diagnosis of the climacterium was confirmed by the finding of elevated urinary gonadotropins.

Calcium balance studies were performed as outlined by Albright and Reifenstein (2). Patients were given a low-calcium diet (103 mg. $\pm$ 10 mg.) for three days prior to the onset of the study, with a daily calcium supplement of 650 mg. in the form of calcium lactate added in four equal doses. This yielded a total daily calcium intake of approximately 750 mg. The calcium tolerance test was carried out according to the method of Schilling and Laszlo (4) and patients were kept on the low-calcium diet for at least two days prior to the test. A dose of 446 mg. of calcium was given intravenously in the form of calcium gluconate over a four-hour period and, although urines were collected and measured for calcium sequentially, the results were reported in terms of the total amount of calcium excreted in the urine during the 24-hour period that included the infusion. For control purposes, calcium balance studies were carried out in the 3 menopausal women with no evidence of osteoporosis, and calcium tolerance tests were performed in the 3 young male and female normal subjects.

The estrogen-androgen tablet administered therapeutically contained 1.5 mg. of piperazine estrone sulfate (equivalent to 0.01 mg. of ethinyl estradiol, or 1.25 mg. of estrone sulfate) and 5 mg. of methyltestosterone. This daily dose was arrived at after attempting various combinations of from 0.75 to 3 mg. of piperazine estrone sulfate and from 2.5 to 10 mg. of methyltestosterone.

Side effects were gratifyingly few; only 2 women showed evidence of temporary *uterine staining* and 3 others complained of some oiliness of the skin. Larger doses of estrogen resulted in a greater incidence of vaginal staining and bleeding, and increased doses of androgen were associated with considerable oiliness of

skin, acne, and hirsutism, particularly when the medication was continued for months and years.

RESULTS

Relief of back discomfort was dramatic; patients uniformly experienced partial amelioration within two to four weeks, and complete or almost complete relief from pain within four to six weeks.

The results of the patient balance studies are illustrated by the following representative case reports:

Patient 1, a 59-year-old white male, complained of pain in the back and flanks. X-ray studies revealed bilateral renal stones and severe osteoporosis of the spine with compression fractures of the tenth, eleventh and twelfth thoracic vertebrae. The 24-hour urinary 17-ketosteroids were normal (11.5 mg.), but gonadotropins were elevated (120 m.u. (mouse units)). The seminal fluid contained only 9,000,000 spermatozoa per ml. On the standard dietary regimen described, which included 750 mg. of calcium a day, the patient showed a daily negative calcium balance to the extent of 120 mg. Six 75-mg. pellets of testosterone and one 25-mg. pellet of estradiol were implanted subcutaneously at the angle of the scapula (5). Two months later, under identical dietary conditions, the patient retained 177 mg. of calcium a day. Eight months later he was restudied while taking one estrogen-androgen tablet daily and, with this medication, he retained 112 mg. of calcium a day.

This patient, who had been a semi-invalid because of back pain, and who had lost 7 inches in stature over the preceding ten years, was able to return to his former occupation. He is now relatively comfortable without any type of back support. In addition to the relief of his back pain, the implantation of pellets restored his sexual ability almost to normal and increased his energy and strength to a marked degree. These added benefits were not nearly so apparent with oral therapy.

From the studies of this and a similar patient one may conclude that, although the negative calcium balance of the male osteoporotic subject may be reversed with oral therapy, pellet implantation is to be preferred because of the concomitant benefits.

Patient 1, a 52-year-old white woman, complained of severe pain in the back. She had been subjected to a panhysterectomy for uterine fibroids sixteen years previously. Findings were normal, except for moderate osteoporosis revealed by spine roentgenograms, low urinary estrogens, and high urinary gonadotropins (over 125 m.u.). On the standard calcium regimen she lost 34 mg. of calcium a day. Two months later, under the same dietary circumstances and while receiving 1.5 mg. of piperazine estrone sulfate three times daily, she retained 13 mg. of calcium a day. Three months later, when the medication had been changed to the estrogen-androgen tablet, she showed a positive calcium balance, to the extent of 54 mg. a day.

The results in the foregoing patient were typical of those in 3 women studied in this way. It is interesting that they all had a negative calcium balance when not treated with steroid hormones, showed a positive calcium balance of small to moderate degree after the initiation of estrogenic therapy, and showed a still greater 24-hour calcium retention when androgen was added to the estrogen.

In order to correlate, if possible, the disappearance of back pain with the state of calcium balance, 2 patients were studied over a long period of time; the following results are illustrative:

Patient 3, a 59-year-old colored woman with severe pain in the back, had been amenorrheic for eighteen years. Roentgoenologic examination of the spine revealed moderate osteoporosis. She was given the low-calcium diet with calcium supplement for five consecutive six-day periods and for a sixth six-day period two months later. During the first six-day period she lost 84 mg. of calcium a day. At that time she was given 1 estrogen-androgen tablet daily and during the next period (the second six-day period, but the first one after medication) she lost 97 mg. of calcium a day. During the third period she lost 80 mg of calcium a day; and during the fourth, 13 mg. of calcium daily. It was during this latter time that she first noted relief in her back discomfort. The following six days (the fifth period) she retained 57 mg. of calcium a day. Two months later, during the sixth period of study, she retained 118 mg. of calcium a day and was completely pain-free.

The results in this patient, as well as in a second in whom this experiment was run, suggest the possibility that relief from back pain affords good clinical evidence of the reversal of the negative calcium balance. This is not surprising, in view of the fact that many of our patients with severe grades of osteoporosis accompanied by compression fractures of the vertebrae experienced clinical improvement after three to six weeks of combined oral steroid therapy, despite the obvious fact that no gross organic changes could have occurred during this brief interval of time.

In an effort to determine the calcium-regulating ability of menopausal women who do not show x-ray evidence of osteoporosis, 3 women were studied. The results in the following patient were typical:

Subject 1, a 58-year-old white woman, complained of nothing but chronic fatigue. Repeated questioning elicited no history of important back discomfort. She had been subjected to a panhysterectomy fifteen years previously. The spine was reported as being normal with no evidence of osteoporosis, on two separate x-ray examinations. Nevertheless, on the standard calcium balance regimen she lost 87 mg. of calcium a day. She was then given one estrogen-androgen tablet each day and two months later showed a positive calcium balance, to the extent of 93 mg. a day.

Our original assumption that postmenopausal women without clinical osteoporosis were somehow better able to handle calcium than those with osteoporosis was not substantiated by these experiments. On the contrary, it would appear that the non-osteoporotic patients lost, on the average, as much calcium as those with obvious roentgenologic and clinical signs and symptoms of osteoporosis. This will be discussed later at greater length.

Intrigued by the apparent simplicity of the calcium tolerance test and the results of Spencer *et al.* (3) in senile osteoporosis, we studied 10 menopausal women with osteoporosis, 3 young control women with regular menstrual rhythm, and 3 healthy young men by this technique. The urinary calcium excretions of the 3 normal women and 3 normal men during the twenty-four hours when the intravenous calcium was administered were 103, 109 and 223 mg. and 190, 210 and 245 mg., respectively; whereas the values for the 10 women with osteoporosis were 239, 301, 313, 329, 375, 383, 392, 395, 399 and 406 mg. In 2 of these patients with calcium outputs of 329 mg. and 375 mg., the values were 233 and 248 mg., respectively, two months after beginning the daily administration of an estrogen-androgen tablet.

The calcium tolerance test appears to be an effective way of demonstrating not only the inability of patients with osteoporosis to handle a calcium load, but also the improvement resulting from therapy.

DISCUSSION

Whereas relief of back pain may be expected early when the osteoporotic patient is treated with an estrogen-androgen combination, roentgenologic evidence of improvement is not to be anticipated for a long period of time. In this group of 62 patients, x-ray evidence of improvement was observed in only 2 women and 1 man who were treated for five years or more. Other patients showed no demonstrable roentgenologic changes in the spine during the periods (up to the seven years) they were followed. It has been suggested that the body contains from 1,100 to 1,500 Gm. of calcium, of which the major part is in the skeleton. It has also been suggested that at least 30 per cent of the calcium in the spine must be lost before calcium deficiency is apparent on x-ray examination. Thus, at least 400 Gm. (400,000 mg.) of calcium must be lost before osteoporosis is sufficiently severe to be recognized on the x-ray film. If the climacteric patient loses an average of 100 mg. of calcium a day, it would take four thousand days, or approximately ten to eleven years before the diagnosis of osteoporosis could be made in this way. Smaller increments of daily loss might delay the appearance of osteoporosis to twenty or twenty-five years. Since the daily gain of calcium after steroid therapy is also small, it is not surprising that relatively few patients in this series showed an increase in calcification of the spine within the seven-year period they were followed.

It would appear that, although back pain may result from vertebral fractures and pressure on the spinal nerves, the usual discomfort of which most patients complain is on a different basis. This is manifested by the clinical improvement which occurs shortly after the institution of steroid therapy, when the negative calcium balance becomes positive, and suggests that withdrawal of calcium from the spine is painful. Osteoporosis appears to be more common and more marked in women than in men, an observation consistent with the great number of cases of severe steroid deficiency in the menopause, in contrast to the smaller number of cases in men at this age.

Although osteoporotic men obtain relief from back discomfort with oral therapy, pellet implantation is preferable because of the concomitant increase in libido and sense of well-being. For this purpose six 75-mg. pellets of testosterone and one 25-mg. pellet of estradiol are recommended. After four months, six testosterone pellets are implanted, without estradiol. This alternation of treatment is advisable, because the effect of the androgen lasts four months, whereas that of estradiol continues for from six to eight months.

In addition to combination steroid-replacement therapy one must pay careful attention to the diet, particularly as it involves the protein, calcium and vitamin content. Support of the spine with a well-fitting back brace is important for at least three to six months, but excessive immobilization must be avoided. Mechanical therapy was carried out on the majority of our reported cases by the

Orthopedic department of Temple University Hospital under the direction of John R. Moore, M.D. This therapy consisted primarily of heavy bracing with a Taylor back brace for three to six months, followed by the wearing of a corset containing extra steel stays. Extension exercises directed towards the spinal musculature were carried on for an indefinite period. Night bracing usually consisted of nothing more than a hard bed or a bed board.

CONCLUSIONS

Postmenopausal women and climacteric men tend to lose calcium at the daily rate of approximately 100 mg. X-ray evidence of osteoporosis may, therefore, not be apparent for from ten to twenty-five years. Back discomfort may, nevertheless, be due to the chronic withdrawal of calcium from the spine. Reversal of the negative calcium balance and relief from the bone pain may be achieved within four to six weeks with 1 daily tablet containing 1.5 mg. of piperazine estrone sulfate (equivalent to 0.01 mg. of ethinyl estradiol or 1.25 mg. of estrone sulfate) and 5 mg. of methyltestosterone. Male patients generally prefer pellet implantation because of the concomitant improvement in strength, sense of well-being, and sexual drive.

The thoughtful clinician should give careful consideration to the possibility of routine administration of an estrogen-androgen tablet every day or every other day to postclimacteric men and women, in order to avoid or delay the development of osteoporosis and perhaps other degenerative metabolic disorders as well. The fear of inducing carcinoma with these hormones in these doses would seem groundless, on the basis of the experience of many clinicians with many patients for many years.

Acknowledgments

The authors are grateful to Abbott Laboratories for the generous supply of piperazine estrone sulfate plus methyltestosterone tablets (Sulestrex-MT) and piperazine estrone sulfate tablets (Sulestrex); and to Schering Corporation for the pellets of estradiol (Progynon) and testosterone (Oreton-F).

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DIAGNOSIS OF ATHEROSCLEROSIS BY PROTEIDOGRAM, LIPIDOGRAM AND GLUCIDOGRAM*

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Paper electrophoresis has recently been added to the many chemical, physicochemical, and physical procedures which yield findings hailed as diagnostic of atherosclerosis.

Low alpha-globulin, high beta-globulin, and normal gamma-globulin have been labeled as typical of the proteidogram in atherosclerosis. This conclusion was based on serum studies in patients with coronary disease with or without recent myocardial infarction and in patients with occlusive femoral atherosclerosis with or without diabetes or nephritis (1). An increase in slow-migrating beta-lipoprotein fractions was found in 33 patients with thrombosed atherosclerotic vessels of the limbs (2). Increased alpha- and beta-globulin in the protein spectrum and increased beta-lipoproteins were recorded in a patient with recent myocardial infarction and hypercholesteremia (3). A shift from alpha-lipoprotein to slower-migrating serum fractions was noted in 2 patients with atherosclerosis (4). Broadening of the beta-lipoprotein range was observed in 21 patients who had had myocardial infarction (5). Six out of 8 patients in whom blood was studied "as soon as possible" after acute infarction showed increased beta-lipoproteins (6, 7). The foregoing results were reported under the heading of "studies in atherosclerosis" and interpreted as diagnostic aids.

It is misleading to separate people with atherosclerosis from those without atherosclerosis by basing the diagnosis on the history of current or past myocardial infarction or any other complication of vascular disease. It is erroneous to use such a criterion for evaluation of diagnostic procedures or therapeutic measures, or for statistics. To support our concept the following report is presented.

MATERIALS AND METHODS

The blood serum of 120 persons was studied by paper electrophoresis. Onto each of three Whatman No. 1 filter-paper strips, an 8-lambda sample of serum was applied. Strips were processed at 7–10°C. for fourteen hours at 3.2 A and 110 V (DC), in a sodium barbital-sodium acetate buffer of pH 8.5 and 0.1 mho. Protein fractions were stained with Bio Blue (8), lipoproteins with Sudan Black (9), and glucoproteins were demonstrated with the periodic acid-Schiff reaction (10). Densitometry, planimetry, and calculations followed. The concentration of total protein was determined by the biuret reaction, of lipids by Bloor's method, and of cholesterol by the Schoenheimer-Sperry method.

The selection of subjects with regard to sex and age is shown in Table 1.

* This study was made possible through a grant from the Delaware Heart Association.

TABLE 1. *Sex and Age Distribution in Four Groups of Subjects*

	No. of Subjects			Age of Males			Age of Females			Age of All Subjects (avge.)
	Male	Female	Total	Min.	Avge.	Max.	Min.	Avge.	Max.	
I. Healthy young and middle-aged persons	27	17	44	16*	37	52	16*	37	48	37
II. Patients with angina	13	7	20	25	50	68*	33	51	70*	50½
III. Patients with recent infarction	20	12	32	34	55	73*	36	57	68*	55
IV. Asymptomatic aged persons	16	8	24	70	79	90	71	79	86	79

* A single individual.

Among the healthy persons (Group I), there were but 3 below the age of 20 years. The majority could be classified as of early middle age. One might assume that they had some degree of atheromatous or even atherosclerotic patching, insufficient to be detected clinically. They were in the latent, asymptomatic phase of "atherogenesis." The patients with angina pectoris (Group II) were middle aged. Their atherogenesis was accompanied by the vasospasm seen in the symptom-rich phase of the disease. (The term "atherosis" could be used for this phase.) The patients with recent myocardial infarction (Group III) were, with respect to age, comparable to the group of patients with angina. They were acutely ill. Their illness was due to tissue anoxia following vascular occlusion, thrombosis, or hemorrhage. They were in the third phase of the disease, in which atherogenesis in the form of more or less extensive atheromatosis and/or atherosclerosis, is complicated by tissue involvement. The asymptomatic aged people (Group IV) had advanced atherogenesis. Judging from results of radiologic and ophthalmic examinations, atherosclerosis exceeded atheromatosis. However, their disease was asymptomatic at the point of examination.

OBSERVATIONS

Abnormal findings should always be analyzed in the light of normal variations. There are distinct fluctuations in the elpherogram from one person to another. There also are fluctuations in the same individual examined on different occasions. A relative change in one fraction results in a relative change in another fraction. Absolute increase or decrease of the total can be caused by a change in any fraction or fractions. Marked deviation of one fraction in even a single subject will alter the minimum or maximum value of this fraction for a whole series, and also influence the average.

Proteidograms. Minimum, average, and maximum values for the four series of subjects are summarized in Table 2. Values for total protein and fractions are expressed in Gm. per 100 ml. of serum and also in per cent.

The sera of the four groups did not differ in total protein content. Compared with the healthy persons (Group I), the other three groups had less serum albumin and more globulin. This was noticeable especially in patients with infarc-

TABLE 2. *Values for Total Protein and Protein Fractions in Four Groups of Subjects*

Group*			TP†	A	G	α_1	α_2	β	γ	A-α_1	G-α_1
I	Minimum	Gm. %	5.35	2.05	2.27	0.26	0.25	0.28	1.03	2.57	1.14
	Average		6.93	3.91	3.26	0.45	0.73	1.05	1.57	3.55	3.35
	Maximum		7.90	4.86	6.39	0.82	1.11	1.89	3.02	6.39	5.54
	Minimum	%	100	30.8	39.5	4.2	3.4	6.1	10.5	38.7	34.6
	Average		100	42.2	57.8	7.2	10.9	15.2	22.0	49.1	50.9
	Maximum		100	60.5	69.2	11.9	15.3	25.9	30.0	65.4	61.3
II	Minimum	Gm. %	4.80	1.79	2.26	0.21	0.36	0.54	0.87	2.00	2.05
	Average		7.30	2.95	4.35	0.47	0.78	1.08	1.57	3.85	3.44
	Maximum		8.85	4.03	5.28	0.71	1.33	1.79	2.77	4.53	4.67
	Minimum	%	100	34.1	43.1	4.1	6.2	9.5	15.1	43.1	36.1
	Average		100	43.1	56.9	6.8	11.5	15.6	22.6	49.9	50.1
	Maximum		100	56.9	65.9	9.2	15.0	23.0	35.1	63.9	56.7
III	Minimum	Gm. %	4.85	1.63	2.98	0.29	0.34	0.56	0.56	2.98	2.22
	Average		7.06	2.71	3.90	0.61	1.12	1.12	1.56	3.33	3.67
	Maximum		7.60	3.57	5.28	1.02	1.18	1.18	2.53	5.39	4.61
	Minimum	%	100	27.6	50.9	4.5	4.5	10.9	10.2	35.7	29.5
	Average		100	38.9	61.1	8.9	13.4	16.5	22.6	47.7	52.6
	Maximum		100	49.1	72.4	13.4	22.7	33.9	33.3	60.4	64.3
IV	Minimum	Gm. %	6.25	2.73	3.56	0.30	0.51	0.83	1.31	2.90	3.16
	Average		7.29	3.08	4.13	0.56	0.75	1.26	1.67	3.64	3.64
	Maximum		8.20	4.24	6.58	0.85	1.05	1.65	1.92	4.76	4.76
	Minimum	%	100	33.0	48.2	3.4	6.9	11.3	19.4	47.3	44.3
	Average		100	42.3	57.7	7.1	10.4	17.3	22.9	49.0	51.0
	Maximum		100	51.8	67.0	11.5	13.4	23.7	27.0	55.7	52.7

* I = healthy young and middle-aged persons; II = patients with angina; III = patients with acute infarction; IV = asymptomatic old persons.

† TP = total protein; A = albumin; G = globulin; α_1 = alpha$_1$-globulin; α_2 = alpha$_2$-globulin; β = beta-globulin; γ = gamma-globulin; A + α_1, G-α_1, for correlation with chemical assays.

tion. In these patients only, was there an increase in alpha$_2$-globulin. Although the average values for gamma-globulin were the same in all four groups, the range for this fraction varied from one group to another.

Lipidograms. Minimum, average, and maximum values for various lipoprotein fractions in the four series are shown in Table 3, together with total serum lipid and cholesterol levels.

An analysis of a lipidogram presents difficulties because of the uneven number of fractions which complicate computation of average values. (In our tables, the sum total of each fraction is in proportion to the total number of patients in each group rather than to the number of patients in whom the particular fraction was present.) Normally, an albumin fraction is rarely present. When present, it is usually fused with the first alpha-fraction (Aα_1). This peak is in a location corresponding to an intermediary position between albumin and alpha$_1$-globulin of the proteidogram. An alpha$_2$- fraction is rarely present. When it is visible, it is close to the position of alpha$_2$-globulin of the proteidogram. In the serum of healthy persons, there are usually three beta-fractions. These are either the two

TABLE 3. *Values for Total Lipid, Total Cholesterol, and Lipoprotein Fractions in Four Groups of Subjects*

Group*	Values (mg./100 ml.)	TL†	TC	$A\alpha_1$	α_2	β_{tr}	β_r	β_l	β_{tl}	β_{ul} §
I	Minimum	360	71	0	0	0	0	12.4	0	0
	Average	470	160	14.3	0.7	20.0	25.1	22.7	14.2	0.8
	Maximum	860	265‡	27.3	10.0	56.8	43.6	43.6	50.0	10.5
II	Minimum	380	107	0	0	0	0	0	0	0
	Average	530	184	12.8	0.6	21.3	25.3	19.1	16.7	4.8
	Maximum	820	239	25.4	12.2	58.4	77.6	34.1	53.1	27.4
III	Minimum	400	89	0	0	0	0	0	0	0
	Average	570	200	13.9	2.9	21.0	22.9	23.5	12.1	3.5
	Maximum	880	207	32.8	35.5	56.2	44.9	40.0	30.0	27.0
IV	Minimum	400	89	3.5	0	0	0	12.9	0	0
	Average	540	134	15.5	0	11.5	19.2	22.7	18.6	12.4
	Maximum	910	270	36.3	0	38.5	29.8	32.8	42.6	48.4

* I = healthy young and middle-aged persons; II = patients with angina; III = patients with acute infarction; IV = asymptomatic old persons.

† TL = total lipid; TC = total cholesterol; $A\alpha_1$ = albumin/alpha$_1$- ; α_2 = alpha $_2$- ; β_{tr} = beta, très rapide; β_r = beta, rapide; β_l = beta, lente; β_{tl} = beta, très lente; β_{ul} = beta, ultra lente lipoproteins.

‡ Three healthy persons had cholesterol levels above 200 mg. per 100 ml. of serum.

rapidly migrating (β_{tr}, β_r) and the first slowly moving (β_l) fractions, or the second rapid (β_r) and the two slow (β_l, β_{tl}) beta-lipoproteins. Rapid fractions are classified as those which occupy roughly the position of beta- or beta$_1$-globulin of the proteidogram. Those fractions which are in either the beta$_2$- or gamma-globulin position of the proteidogram are labeled as slow-moving beta-lipoproteins. The stationary fraction (β_{ul}), which presumably represents chylomicrons, is found close to the place where the serum was applied to the filter paper.

The frequency with which various lipoprotein fractions were observed in the four groups of subjects is seen in Table 4.

The average total amounts of alpha-, rapid beta-, slow beta-, and stationary beta-fractions, expressed as percentages of total lipoprotein, are presented in Table 5.

Compared to the results in healthy young and middle-aged persons there was an increased incidence of the stationary beta-lipoprotein fraction (β_{ul}) in patients with angina and those with infarction. In the group of old people, the incidence of this fraction was even higher. The relative amounts of this fraction paralleled the increased frequency. In the aged, there was also a shift from rapid to slow beta-fractions. The incidence of alpha$_2$-lipoprotein fraction declined in patients with angina, and in the group of aged this fraction was never found. Patients with acute infarction did not follow the trend: the alpha$_2$-lipoprotein fraction was present often; moreover, the most rapid beta-fraction occurred more frequently in patients with infarction than in other groups.

Total serum lipoprotein, as estimated from the total area of filter paper stained

TABLE 4. *Percentage Frequency with which Various Lipoprotein Fractions Occurred in Four Groups of Subjects*

Group*	$A\alpha_1$†	α_2	β_{1r}	β_r	β_1	β_{tl}	β_{ul}
I	98	20	62	95	100	69	12
II	95	5	45	90	80	75	30
III	97	66	78	94	100	69	28
IV	100	0	50	83	100	83	67

*† *See* footnotes to Table 3.

TABLE 5. *Average Amounts of Fractions Expressed in Percentages of Total Lipoprotein in Four Groups of Subjects*

Group*	$A\alpha_1 + \alpha_2$†	$\beta_{1r} + \beta_r$	$\beta_1 + \beta_{tl}$	β_{ul}
I	15.0	45.1	36.9	0.8
II	13.4	46.6	35.8	4.8
III	16.8	43.9	35.6	3.5
IV	15.5	30.7	41.3	12.4

*† *See* footnotes to Table 3.

TABLE 6. *Average Blood Cholesterol Levels (mg./100 ml.) in Males and Females in Four Series of Subjects*

Group*	Males	Females	Total
I	188	168	160
II	189	185	184
III	200	185	200
IV	129	154	134

* *See* Table 1.

with Sudan Black, was the same in Groups I, II and IV. In the serum of patients with acute myocardial infarction, however, the area was 12 per cent greater. The tendency toward multiple fractions was increased in patients with angina or infarction—four beta-lipoprotein fractions were present as often as three. Total lipid levels were too variable for valid analysis.

There was no difference between males and females in either of the four groups of subjects, no matter which way the lipidogram was analyzed. Except for the group of aged people, the blood cholesterol level of men was slightly higher than that of women. This is illustrated in Table 6.

Glucidograms. Minimum, average, and maximum values for the protein-bound carbohydrate fractions are listed in Table 7.

As a rule, the normal glucidogram has five fractions. The first three fractions ($A\alpha$, α_1, α_2) are all alpha-globulin fractions. Their locations in the proteidogram are those of albumin-, alpha$_1$-, and alpha$_2$-peaks, respectively. In about one fifth of all sera there are two beta-fractions. Normally, the magnitude of the three alpha-globulin peaks is 1:2:3.

TABLE 7. *Values for Glucoprotein Fractions in Four Groups of Subjects*

Group*	Per Cent	Aα†*	α_1	α_2	β	γ
I	Minimum	0	10.9	20.4	14.7	8.2
	Average	9.0	23.6	32.6	25.2	16.3
	Maximum	20.6	32.0	36.4	32.4	32.8
II	Minimum	0	0	22.8	16.6	6.9
	Average	8.4	24.2	34.2	23.7	12.6
	Maximum	17.7	30.4	38.4	33.9	34.8
III	Minimum	0	13.5	24.6	12.2	4.6
	Average	7.2	24.9	37.2	21.2	9.6
	Maximum	13.5	36.1	46.4	33.3	16.7
IV	Minimum	4.4	5.3	29.2	17.2	7.4
	Average	8.4	10.8	36.0	23.3	12.2
	Maximum	14.1	28.0	47.4‡	32.0	23.4

* I = healthy young and middle-aged persons; II = patients with angina; III = patients with acute infarction; IV = asymptomatic old persons.

† A α = albumin/alpha- ; α_1 = alpha$_1$- ; α_2 = alpha$_2$- ; β = beta- ; γ = gamma-glucoprotein. (First alpha-fraction in albumin position.)

‡ Two patients with an alpha$_2$-fraction in excess of 40 per cent. Both had encephalomalacia. Without these 2, the maximum for the group would have been 36.7, and average value would have been 30.7 per cent.

The glucidogram of patients with angina or that of aged persons did not differ essentially from that of healthy persons, in our series. (Exceptions are noted in footnotes to Table 7.) There was a marked increase in alpha$_2$-glucoprotein, a moderate rise in alpha$_1$-glucoprotein, and a moderate decline in all other fractions in the sera of patients with myocardial infarction, as well as in the sera of patients showing tissue destruction other than myocardial.

DISCUSSION

Results of our studies should be analyzed from two perspectives: 1) the stage of vascular disease, and 2) the age of the subjects.

The proteidogram and the glucidogram are markedly altered in patients with acute myocardial infarction. They are not significantly changed in asymptomatic young or aged persons or in those with angina pectoris. The lipidogram of patients with infarction differs from that of all other subjects by the increase in the slow alpha-fraction (α_2) and in the very fast beta-fraction (β_{tr})—that is, in the fractions in which most of the serum cholesterol is incorporated. With regard to frequency and quantity of stationary beta-lipoproteins (β_{u1}), patients having myocardial infarction closely resemble patients having angina without infarction. With progressive age, there is an increase in stationary beta-lipoproteins (chylomicrons). In the aged, there is also a tendency toward an increase in slow-migrating beta-fractions and a decrease in fast-migrating beta-fractions. The decline of alpha$_2$-lipoprotein likewise parallels advancing age.

Electrophoretic deviations such as those observed in the serum of middle aged patients having acute myocardial infarction were not found in the serum of

middle-aged patients having angina pectoris without infarction, nor in young or aged persons with mild or even severe but asymptomatic vascular disease (atherogenesis). Thus, it would be erroneous to interpret deviations found in the serum of patients with acute myocardial infarction as being characteristic of "atherosclerosis."

SUMMARY

1. Serum proteidograms, lipidograms and glucidograms were obtained on serum from 44 healthy young and middle-aged adults, 20 middle-aged patients with angina pectoris, 32 middle-aged patients with myocardial infarction, and 24 aged persons who had asymptomatic arterial disease.

2. Serum of patients with angina pectoris differed from that of healthy persons only slightly. The picture was that of moderate hypoalbuminemia and hyperglobulinemia, a 75 per cent decline in alpha$_2$-lipoprotein and a threefold increase in frequency plus a fivefold increase in the quantity of stationary fraction. The glucidogram was not altered.

3. Serum of patients with acute myocardial infarction differed markedly from that of the other groups studied. Only so far as stationary "beta-lipoprotein" was concerned did the data parallel those obtained in patients with angina pectoris who were of comparable age. There was severe hypoalbuminemia and hyperglobulinemia. The latter was due to a sharp rise in alpha$_2$-globulin. Alpha$_2$-lipoprotein was observed three times as frequently as in other groups. The incidence of the rapid beta-lipoprotein fraction was also higher. In the glucidogram, there was a pronounced increase in the alpha$_2$-fraction and a mild increase in the alpha$_1$-fraction. Other fractions were decreased.

4. The serum of old persons with asymptomatic vascular disease differed from normal only slightly in the proteidogram and not at all in the glucidogram. There was moderate hypoalbuminemia and hyperglobulinemia. In the lipidogram, the stationary fraction (chylomicrons) was found five times more frequently and in amounts fifteen times greater than in the serum of healthy young adults. Slow-moving beta-lipoproteins were increased, and fast-moving beta-fractions were decreased in amount.

5. A decrease in the alpha$_2$-lipoprotein fraction and an increase in the stationary beta-lipoprotein fraction paralleled advancing age. Correlation with "atherosclerosis" is permissible only on the basis of experience concerning the increased frequency with which plaques are found in arteries with advancing age.

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ORAL MERCURIAL DIURESIS

JEROME G. KAUFMAN, M.D., ARTHUR BERNSTEIN, M.D., FRED WEISS, M.D., EMANUEL KLOSK, M.D., FRANKLIN SIMON, M.D. AND HAROLD S. FELDMAN, M.D.

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The constant search of the pharmacologist and clinician for a safe, acceptable and effective oral diuretic points up the continued need for such a product and its extreme usefulness in medical practice. Certainly, an oral preparation has obvious advantages:

1. Diuresis at a slow and regular rate with the avoidance of acute, often uncomfortable, diuresis (1) which frequently results in marked alterations of fluid and electrolyte balance. Rapid, intense diuresis has been known to induce attacks of gout (2), tetany (3), cerebral thrombosis (4), and digitalis intoxication.

2. Ease of administration, which means not only greater acceptability by the patient at less expense than professionally administered medication, but also the absence or reduced frequency of painful injections when the oral preparation is effective. The use of a potent parenteral product obtained from a multiple-dose vial and given subcutaneously as one would give insulin (5) was a great step forward in diuretic therapy. An oral preparation with the required features, used in conjunction with such a product, would make a valuable combination. Acceptability by the patient determines in very great part the usefulness of a diuretic, and thus the medical control of the congestive picture.

PHARMACOLOGY

Combination with various members of the xanthine group or a change of the mercury linkage in the molecule has resulted in many new mercurial compounds derived from older, already tried, preparations.

Merpurate[1] is the hydrated crystalline double salt of calcium N-(-methoxymercuripropyl)-2-pyridone-5-carboxylate and calcium theobromine. This mercurial diuretic is a chemical entity containing 39.25 per cent theobromine, 4.3 per cent calcium, 9.8 per cent water and 45.58 per cent of N-(methoxy-mercuripropyl)-2-pyridone-5-carboxylate. The elemental mercury content of Merpurate has been determined as 21.8 per cent, based on the crystalline double salt.

ANIMAL STUDIES

Mongrel dogs after a period of quarantine and observation testing were fed varying doses of Merpurate ranging from 12 to 40 mg. per kilogram of body weight for approximately six months. During this, time weights, renal function and hematologic pictures were determined and evaluated for possible toxic effects secondary to prolonged high dosage of Merpurate. From the data obtained it was evident that Merpurate had little, if any, toxic effect on kidney

[1] Merpurate tablets were supplied by Maltbie Laboratories Division, Wallace & Tiernan Incorporated, Newark 1, New Jersey.

function or blood morphology. There were no abnormal changes in growth and development. At the conclusion of the studies all animals were sacrificed and all organs studied grossly, microscopically, and chemically for mercury content. Gross and microscopic examinations of the vital organs showed no evidences of cellular degeneration or necrosis.

The kidney, heart and liver were analyzed for mercurial content by colorimetric methods; and no unusual or unexpected tissue affinity was demonstrated. In the spleen, brain, lung and bone no mercury was found.

STUDIES ON PATIENTS WITH CONGESTIVE HEART FAILURE

Materials and methods

Thirty ambulatory cardiac patients were used for this study (Table 1). They demonstrated the usual signs and symptoms of excess fluid accumulation in the tissues, secondary to well established chronic congestive failure. The congestive failure was due to coronary arteriosclerosis in 17 subjects, to combined hypertension and arteriosclerosis in 10, to rheumatic heart disease (inactive) in 2, and to syphilitic heart disease in 1. All these patients were digitalized and were presumably receiving low-salt diets. As expected, a review of the individual cases indicated that there was no strict adherence to a truly acceptable low-sodium diet (6). However, since a so-called low-salt diet is almost universal in all ambulatory patients, it offered us a more realistic picture of the effectiveness of the product to be tested. Some of our cases undoubtedly might have been controlled with a strictly salt-free diet without any diuretic, but our past experience showed that in general parenteral medication was absolutely necessary and we did not wish to stress a more strict diet during our period of observation.

Ambulation was continued and encouraged in all instances. These patients reported to the cardiac out-patient clinic of the Newark Beth Israel Hospital or to our private offices. All had been receiving parenteral mercurial diuretics at least weekly in order to maintain adequate cardiac compensation. Therapy, other than a change in the diuretic from parenteral to oral, was not altered during the present study.

Depending on the condition of the patient, one of four types of tablet administration was employed in the switch-over from injection to oral administration of mercurial preparations. When necessary the patient was changed from one schedule to another without the intermediate use of injectable diuretics. The dosage schedules were as follows: 1) sixteen tablets per week, *i.e.*, one tablet after meals and at bedtime on Monday, Tuesday, Thursday and Friday; 2) thirty-two tablets per week, *i.e.*, two tablets after each meal and two at bedtime on Monday, Tuesday, Thursday and Friday; 3) twenty-eight tablets per week, *i.e.*, one tablet after meals and one at bedtime, daily; and 4) fifty-six tablets per week, *i.e.*, two tablets after each meal and two at bedtime, daily.

All patients were observed at least weekly by one of us and response to therapy was evaluated as far as possible by means of the patient's immediate reaction to administration, subjective comment of diuresis and relief of congestive signs and symptoms, and particularly by loss or gain of weight as determined at every visit.

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TABLE 1

Patient	Age	Sex	Diagnosis	No. of Injections of Mercurial per Wk.		Duration of Exp. (months)	No. of Tablets of Oral Mercurial per Wk.	Response	Toxic Reactions	Placebo	Reaction on Placebo	Notes
				Before exp.	During exp.							
1. I. N.	68	F	HCVD*	1	0	6	28	Good	None	12 wks.	Cardiac failure recurred	Present condition good
2. P. G.	70	M	ASHD	2	0	11	56	Good	Mild loss of appetite	Not used	—	Present condition good
3. W. C.	58	M	HCVD	2	0	25	56	Good	None	6 wks.	Cardiac failure recurred	Present condition good
4. F. N.	73	F	ASHD	1	0	4	28	Good	None	Not used	—	Did not return to clinic
5. J. S.	72	M	ASHD	2	0	4	56	Good	Loss of appetite	Not used	—	Refused pills
6. S. R.	78	M	ASHD	2	0	14	28	Good	None	Not used	—	Died; coronary occlusion
7. G. P.	72	M	SHD	1	0	17	32	Good	None	9 wks.	Cardiac failure recurred	Died
8. S. E.	76	M	ASHD	2-3	0	22	56	Good	Vomiting	6 wks.	Cardiac failure recurred	Died
9. L. H.	75	M	ASHD	2-3	0	16	56	Good	Loss of appetite	Not used	—	Present condition good
10. A. W.	75	F	ASHD	1	0	24	28	Good	None	8 wks.	Cardiac failure recurred	Present condition good
11. C. B.	58	F	HCVD	1	0	8	32	Good	None	8 wks.	No reaction	Released from experiment
12. C. S.	65	M	HCVD	3	1	15	56	Good	None	Not used	—	Condition good
13. E. V.	80	F	ASHD	2	0	12	56	Good	None	6 wks.	Cardiac failure recurred	Died; fractured hip; autopsy
14. S. Q.	70	F	ASHD	3	1	16	56	Good	None	Not used	—	Diabetes; condition good

14. S. Q.	70	F	ASHD	3	1	16	56	Good	None	Not used	—	Response good
15. C. M.	70	M	ASHD	3	1	16	56	Good	None	Not used	—	Response good
16. G. C.	58	M	HCVD	2	0	13	56	Good	None	5 wks.	Cardiac failure recurred	Died; cerebral accident
17. D. O.	65	F	ASHD	2	0	15	56	Good	None	5 wks.	Cardiac failure recurred	Rheumatoid arth.; response good
18. P. R.	41	F	RHD	2	0	9	56	Good	None	Not used	—	
19. A. G.	58	M	ASHD	1	0	18	28	Good	None	Not used	—	Response good
20. S. E.	78	M	ASHD	3	0	11	28	Good	None	8 wks.	Cardiac failure recurred	Duodenal ulcer; became too weak to come to clinic
21. J. F.	52	M	RHD	1	0	5	32	Good	None	Not used	—	Lost to clinic
22. J. A.	64	M	ASHD	1	0	12	32	Good	None	Not used	—	Lost to clinic
23. F. M.	70	F	ASHD	1	0	6	28	Good	None	Not used	—	Likes injection better
24. M. K.	56	F	HCVD	1	0	8	16	Good	None	Not used	—	Excellent response
25. A. A.	78	M	HCVD	1	0	12	28	Good	None	Not used	—	On another oral mercurial poor result
26. H. W.	79	M	HCVD	1	0	24	32	Good	None	1 wk.	Cardiac failure recurred	Surgical intervention; continued good response to oral mercurial
27. D. K.	67	F	ASHD	1	0	26	28	Good	None	None	—	Excellent response
28. A. A.	76	M	ASHD	1	0	20	28	Good	None	None	—	Excellent response
29. M. K.	68	M	HCVD	1	0	14	28	Good	None	6 wks.	No cardiac failure	Released from experiment
30. F. S.	63	M	HCVD	1	0	17	28	Good	None	None	—	Excellent response

* HCVD—Hypertensive Cardiovascular Disease. ASHD—Arteriosclerotic Heart Disease. SHD—Syphilitic Heart Disease. RHD—Rheumatic Heart Disease.

Note was also made of the patient's responses as observed by the medical personnel.

All patients were further studied at regular intervals by means of electrocardiograms, chest roentgenograms, blood urea nitrogen determinations, complete blood counts and urinalyses.

When possible, placebo replacement was attempted with a tablet that resembled in all respects the active medication, and was continued until there was obvious increasing cardiac failure. In all cases in which failure developed during placebo administration, elimination of the edema was attempted by oral mercurial therapy alone.

OBSERVATIONS

Twenty-five of the 30 patients who were given the oral diuretic were successfully maintained without even the occasional addition of a parenteral diuretic, although at times it was necessary to change from a more limited to a more intensive dosage in order to improve control of increasing failure. The diuretic response, when noted as such by patients, was considered comfortable and in no way exhausting; it was not of such magnitude as to cause excessive loss of sleep as a result of frequent urination. In only 4 cases was it necessary to resort to parenteral diuretics in order to control an increasingly severe failure. Patient acceptability was unusually good and no severe toxic reactions were noted. Some patients took the drug for over two years during this study. Anorexia was not uncommon, but was of significant degree in only 4 patients; a reduction in dosage resulted in disappearance of the anorexia without loss of cardiac compensation. One patient with chronic uremia and a blood urea nitrogen level of 90 mg. per 100 cc. was given the drug for over twenty-two months. Occasional vomiting had been noted prior to this oral therapy; surprisingly, it was not increased during the period of observation, nor was there any increase in renal failure. In 2 patients diarrhea was noted, which subsided with a reduction in dosage and did not recur with a return to higher dosage. When specifically inquired about, vague abdominal complaints were commonly reported during this time by the majority of the patients, but in most instances these complaints had also been noted prior to the observation period and were not increased during oral mercurial therapy. One patient with a known peptic ulcer continued to take Merpurate without any untoward gastro-intestinal complaints. One patient who had severe leg cramps during treatment with injectable diuretics, and who was not able to achieve satisfactory control with a carbonic-anhydrase inhibitor, was maintained comfortably on oral Merpurate. Another patient underwent a successful transurethral resection while being maintained on the drug.

Eleven patients were given placebo after discontinuance of all diuretics; 9 began to show increasing cardiac failure, both subjectively and objectively; in the other 2, control was maintained. In all those in whom failure developed, a satisfactory state of control was achieved upon reinstitution of oral Merpurate therapy alone.

DISCUSSION

In recent years the continued search for a safe, tolerable and effective oral diuretic has presented to the clinician a wide variety of products. The search was first seriously begun by Batterman *et al.* (7) and continued by many other investigators (8–13). All oral mercurial diuretics have had the disadvantage of a large number of untoward side effects. Merpurate contains 20 mg. of mercury per tablet, as compared to the usual dose of 10 mg. per tablet found in most other oral mercurial diuretic tablets. On this basis one might expect a greater incidence of side reactions with the use of Merpurate. However, although the mercury content per tablet is great, and the number of tablets used frequently was large, we did not notice any appreciable incidence of unpleasant side reactions. Based on previous experience with other oral mercurial diuretics, we found Merpurate more tolerable in effective dosage than other mercurials. An occasional gastro-intestinal upset such as nausea, vomiting, anorexia, or diarrhea was usually controlled by a temporary cessation of drug therapy and reinstitution in reduced dosage.

In a study lasting over two years, we found that Merpurate could replace parenteral diuretic therapy in every case, and in no instance was it necessary to discontinue its use, either because of unpleasant side effects, ineffectiveness, or toxicity as determined by repeated renal, hematologic and electrocardiographic studies.

The effectiveness of Merpurate was established by observations with the use of placebo in 11 patients. Nine of the 11 began to show increasing cardiae failure—a demonstration of both the need for, and the effectiveness of the diuretic.

CONCLUSIONS

1. A clinical evaluation of a new oral mercurial diuretic (Merpurate) has been carried out in 30 cardiac patients, using varying dosages for periods exceeding two years.

2. Individual dosage schemes were determined for each patient but failure could in almost every case be controlled after complete withdrawal of parenteral diuretic by the substitution of the oral diuretic in a dosage of 16 to 56 tablets per week (320 to 1,120 mg. of mercury).

3. No unusual or unduly severe untoward reactions were noticed and in no case was it necessary to discontinue the tablets. Renal, hematologic, and electrocardiographic studies repeated periodically for as long as two years failed to reveal any important toxic reactions during either acute or chronic administration.

4. This study indicates that Merpurate in adequate dosage is a safe, patient-acceptable, and effective oral diuretic which can replace parenteral diuretics in most patients.

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STUDIES OF THE AGED: THE SELECTION OF ELDERLY PATIENTS FOR MAJOR SURGICAL OPERATIONS

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In order to decide how aggressively to treat disease or deformity in aged individuals one must have certain fundamental information. The patient's ordinary expectation of life should be known. The natural history of his disease should be understood and the influence of associated complicating factors on the risk of treatment should be evaluated. It is evident that the decision regarding the form of treatment can not be based on statistical information alone, but clinical judgment is often based on knowledge of probabilities supplied by these data.

The life expectancy of elderly persons is often higher than is realized. The data in Table 1 were furnished by the Union Central Life Insurance Company. We have found them helpful in considering the wisdom of trying to cure malignant tumors as well as the desirability of correcting benign conditions in certain age groups. It does not seem reasonable for an otherwise healthy person of 70 years to put up with the discomfort and potential hazard of a hernia for the ten years he expects to live, if the condition can be corrected with reasonable safety.

When one has considered the life expectancy of a patient in relation to the urgency and importance of his disability, the next question is whether the operation can be performed with reasonable safety. Between January 1, 1952 and December 31, 1954 at the Mary Imogene Bassett Hospital, 338 major operations were performed on patients over 69 years of age. Of these patients, 30 or 8.9 per cent died. In Table 2 are listed the operations which were survived by these elderly patients; in Table 3 are the operations which proved fatal.

It is apparent that the type of operation was not the determining factor in the mortality rate, inasmuch as many of the more complex operations carried a lower mortality rate than the relatively simple procedures. Enterostomy, for example, had the highest mortality rate—a third of the patients died. The high mortality rate associated with enterostomy, internal fixation of fractures, and operations on the urinary bladder is clearly associated with failure to eliminate the poorest-risk patients from these groups. Many of the enterostomies and cystostomies were performed on moribund patients in order to make their last days more comfortable.

The methods which we have used to select patients for operation can best be described by listing the contraindications according to the systems involved. A careful history and physical examination, x-ray film of the chest, electrocardiogram, hemogram, urinalysis, and estimation of the blood urea nitrogen and fasting blood sugar levels are considered the basic requirements for evaluation

TABLE 1

Expectation of Life at Various Ages

Age	Complete Expectation of Life in Years
70	10.0
75	7.6
80	5.7
85	4.3
100	2.1

(Union Central Life Insurance Co.)

TABLE 2

Types of Operations Survived by Elderly Patients

Operation	Number
Operation on urinary bladder (including prostatectomy)	62
Surgical reduction of major fracture	50
Resection of part of gastro-intestinal tract	46
Hernioplasty	44
Operation on biliary tract	29
Plastic operation	20
Enterostomy	12
Mastectomy (4 simple, 8 radical)	12
Major amputation	8
Miscellaneous	25
Total	308

TABLE 3

Types of Operations Which Were Fatal in Elderly Patients

Operation	Number
Surgical reduction of major fracture	6
Operation on urinary bladder	6
Enterostomy	6
Resection of part of gastro-intestinal tract	4
Accidental trauma (equivalent to major operation)	2
Hernioplasty (ventral, with resection of gangrenous bowel)	1
Major amputation	1
Plastic operation	1
Radical neck dissection	1
Laparotomy for exploration	1
Laparotomy for drainage of abscess	1
Total	30

of the patient's physical condition. Other studies are undertaken if they are indicated.

GENERAL CONDITION

Under this heading are considered the various abnormalities which involve the body as a whole or the patient as a psychobiologic entity.

In reviewing the records of our elderly patients we tried to estimate the degree of bodily and mental vigor which each possessed before he became ill. We were unable to gather data which were of statistical significance, but we have the impression that elderly people whose minds are alert and who are active in their personal and community affairs have a much better chance of surviving operation than those with dulled wits and lethargic bodies. It is our further impression that the active individual is a better candidate for surgery, not because he has better protoplasm but because he tends to consult his physician sooner and is better able to give an accurate history and to participate in the activity of his preoperative and postoperative management.

The nutritional status of the patient can best be estimated by considering his dietary history. Except in situations of considerable emergency, we prefer to postpone operation until a normal blood volume has been restored and vitamin deficiencies have been corrected. If the protein content of the tissues has been depleted, such a deficit can not be corrected in less than several weeks by feeding a diet high in protein and amino acids. Therefore, elective surgery should be postponed for a month or more until the general body pool of protein has been refilled and such filling has been reflected in an increase in the protein content of the plasm. If surgical treatment is urgently needed, however, much can be accomplished by the administration of blood and concentrated serum albumin over a period of several days before operation. In spite of the many reports in the literature describing the value of estimation of blood volume by dye dilution, we have not had satisfactory experience with this method in dealing with clinical problems. There are no reliable figures of normal blood volume in the aged. Furthermore, when basing the calculation of normal blood volume on body weight, we do not know whether to use the weight at the time of admission, the patient's reported maximum weight before the onset of the illness, or something in between. We have been unwilling, therefore, to administer blood in an attempt to achieve a theoretically normal volume without knowing what is actually normal. In practice we have found that a history of inadequate diet, of abnormal fluid loss such as by diarrhea or vomiting, of recent loss of weight, a disturbed electrolyte pattern, or an abnormal hemoglobin concentration indicate the need of replacement therapy. The amount of blood and electrolyte solution to be given is determined by the patient's response to therapy. It is well recognized that there may be considerable deficit in the red cell mass in the face of a relatively normal hemoglobin concentration. If this is suspected, blood is given until a definite rise in the hemoglobin concentration can be detected, after dehydration has been overcome.

There are no reliable data available on the relationship of obesity to post-

operative complications. We share the widely held clinical impression that fat people are more likely to have postoperative pulmonary complications and phlebothrombosis. Therefore, we prefer to avoid purely elective surgery in these patients. If an operation is needed, however, it should not be withheld solely because of obesity, but special precautions must be taken to prevent complications.

URINARY SYSTEM

Functional disorders of the urinary tract have not been an important source of trouble in our series of elderly patients. The major cause of renal azotemia in this age group has been obstruction of the vesical neck by prostatic hypertrophy. This condition is usually reversible by the institution of adequate drainage, and elective operations are postponed until maximum improvement has occurred. Infection of the urinary tract is a more serious problem. It accounted for the death of 2 patients and was a contributing cause of death in another.

Elevation of the blood urea nitrogen level above 30 mg. per 100 cc., or the excretion of urine of fixed specific gravity, are readily detectable signs of diminished renal reserve. If severe renal damage is present, we advise against purely elective surgical procedures. However, except in the presence of extreme uncorrectable azotemia, operations for malignant tumors, for the relief of pain, for the relief of obstruction of a hollow viscus, or for similar urgent reasons, should be undertaken after due consideration.

When infection of the urinary tract is present, investigation must include culture of the urine and determination of the sensitivity of the infecting organism to the available antibiotics. It is wise in addition to be sure that there is no obstructing lesion in the tract which contributes to the persistence of the infection. Except in an emergency, needed surgical treatment should await the control of such infection. Operations on the urinary tract itself may have to be performed in spite of infection, but adequate treatment by drainage and antibacterial medication should precede surgical intervention.

RESPIRATORY SYSTEM

Complications arising in the respiratory system are a frequent cause of death in elderly patients. In our series, among the 30 patients who died, 63 per cent had postoperative respiratory complications; among the 308 survivors, only 19 per cent had these complications. This difference is statistically significant.

In an effort to determine whether or not there was a critical level of pulmonary function we studied our patients with respect to these two categories—those who survived and those who died after operation. The incidence of chronic pulmonary disease in these groups was compared and the significance of their difference tested by the chi-square method. Of the patients who survived, 47 or 14 per cent had chronic pulmonary disease; this diagnosis was made in 8 or 27 per cent of those who died. By standard statistical tests it can be shown that there is greater than 5 per cent probability that this difference was due to

chance alone. We were thus unable to demonstrate a significant influence of chronic pulmonary disease on operative mortality. This is not to say that pulmonary disease is not an important factor in the evaluation of these patients. Its presence must be detected and its type determined. We believe that one of the reasons why the mortality rate was not higher in patients with chronic pulmonary disease was because of the active treatment they received before and after operation. Chronic pulmonary disease which is reasonably well compensated is not a contraindication to extra-thoracic operations if its presence is known and if adequate treatment is instituted. The evaluation of candidates for pneumonectomy is outside the scope of this paper.

CARDIAC SYSTEM

Cardiac complications were an important cause of death. They occurred in only 0.6 per cent of the patients who survived, but in 27 per cent of those who died.

In an effort to determine what types of cardiac disease had an important influence on postoperative mortality, we again divided the patients into those who survived and those who succumbed after operation, and compared the characteristics of each group.

Cardiac disease was diagnosed only when there was functional impairment, *i.e.*, congestive failure or a history of failure, angina pectoris, cardiomegaly, or a major electrocardiographic abnormality. Of the entire series, 182 persons or 54 per cent had objective evidence of cardiac disease. The incidence was not significantly different in the two groups; it was present in 49 per cent of those who lived and in 70 per cent of those who died. Of the various manifestations of cardiac disease, however, two seemed to have had prognostic significance. Angina pectoris was present in only 5 per cent of the surviving group, but in 13 per cent of those who died. Major electrocardiographic abnormalities were found in 37 per cent of the survivors, but in 63 per cent of those who died. Thus a history of angina pectoris or the finding of an abnormal electrocardiogram occurred with significantly greater frequency among the patients who succumbed after operation (Table 4). The other manifestations of cardiac disease are also listed in Table 4.

TABLE 4

Manifestations of Cardiac Disease

Manifestation	Living		Dead		Statistically Significant
	No.	%	No.	%	
Failure	29	8.8	5	16.7	No
History of failure	37	11.2	5	16.7	No
Angina pectoris	16	5.2	4	13.3	Yes
Hypertension	117	35.6	13	43.3	No
Cardiomegaly	114	34.6	14	46.7	No
Abnormal ECG	121	36.7	19	63.3	Yes

It is our opinion that the presence of cardiac disease does not in itself constitute a contraindication to needed surgery in an aged patient. However, extreme caution should be used in recommending elective surgical procedures for those persons who have a history of angina pectoris or whose electrocardiograms show signs of advanced myocardial degeneration. Whenever possible, operation should be postponed for two or three months after an episode of acute myocardial infarction. If congestive failure is present, operation should be postponed when possible until maximum benefit has been attained from the administration of digitalis, diuretics and other measures used to improve cardiac function.

VASCULAR SYSTEM

Aside from coronary artery disease, arterial insufficiency was not a complicating factor in our series. If there is a high degree of occlusion of the peripheral arteries, surgical procedures (other than amputation or direct surgical attack on the occluded artery) should be avoided on the extremities.

Spontaneous venous thrombosis occurred in 19 of our elderly patients. A diagnosis of pulmonary embolus was made 7 times in patients who survived. In no case in this series were we able to prove that death resulted from pulmonary embolus, although it was suspected in 3 patients who died suddenly but on whom autopsy was not permitted.

In general, we do not deny needed operation to patients who have a history of venous thrombosis. Patients past middle age who have any type of peritonitis are considered to be likely candidates for phlebothrombosis; therefore, we institute anticoagulation therapy after operation. A similar precaution is taken with obese patients who have had a laparotomy, with patients who may be confined to bed for a long period of time, and with those who have a history of venous thrombosis.

ENDOCRINE SYSTEM

Diabetes mellitus is the most common of the serious endocrine disturbances in elderly patients. In itself, it does not constitute a contraindication to needed surgery. Its presence, however, should make one evaluate with special care the condition of the patient's arteries in general, and his coronary arteries in particular, before surgical treatment is decided upon. There are few operations which should be undertaken in the presence of uncontrolled diabetes. All but the most urgently needed can be postponed at least a few hours until acidosis and electrolyte imbalance are corrected. In the presence of infection, it may be necessary to operate in spite of imperfectly controlled diabetes, but the acidosis should at least be corrected beforehand. In none of our patients was diabetes a significant contributing cause of death.

DISCUSSION

From the account of our experience with elderly patients it is apparent that there are few absolute contraindications to needed surgery. There is, however,

a higher mortality rate among the elderly than among younger individuals. During the time these data were being collected, the mortality rate among 1,073 consecutive patients less than 70 years of age undergoing major operations in this hospital was 1.9 per cent, whereas in our series of patients over 69 the mortality rate was 8.9 per cent. This significant difference is partly accounted for by the fact that many of the operations which carried a high mortality rate in the elderly group, although relatively simple ones, were performed in order to make the patient's last days more comfortable. Furthermore, a greater number of serious operations and fewer elective ones were performed on the elderly patients than on the younger ones.

Complications of the cardiac and respiratory systems were the most frequent cause of death in our patients. We have been unable, however, to establish a critical level of functions which might help to select the patient who is likely to withstand a major operation, other than to indicate that a severe degree of coronary artery disease is a relatively bad prognostic omen.

SUMMARY

Our experience at the Mary Imogene Bassett Hospital with 338 patients over the age of 69 has led us to the following conclusions:

1. Although the risk from surgical intervention is greater for patients over the age of 69 than it is for younger ones, there are no absolute contraindications based on age.

2. A complete appraisal of the elderly patient's condition is necessary in order to decide whether or not operation is warranted, and in order to guard against fatal complications in the period after operation.

Acknowledgment

The authors express their appreciation to Dr. John C. Mithoefer of the Cardio-Pulmonary Laboratory of the Mary Imogene Bassett Hospital for his help in the statistical analysis of the data presented.

HOST-TUMOR ANTAGONISM. II. HORMONE DEPENDENCY OF CERTAIN CANCERS

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A cancer may be defined as a new growth of cells, autonomous in nature, and serving no useful function (1). The fact that no useful function is served distinguishes a tumor from a reparative process. The question may well be asked: Is a tumor really autonomous? Since the advent of hormone therapy, it is known that certain tumors are dependent on hormones for their growth—at least for a period of time.

In cancers, not only is growth abnormal: organization, differentiation and function of the cells are likewise abnormal (1).

Two types of cancer may be considered to be hormone-dependent, namely mammary and prostatic. Stewart (2) believes that spontaneous alteration of the hormonal environment may explain some instances of long evolution of cancer, especially of the breast and prostate. The incidence of clinical breast cancer has two peaks. The first is in the premenopausal period (when the growth is most frequently detected); then there is a sharp decrease during the menopause, followed by a second distinct peak. Stewart suggests that the menopause provides an altered hormonal environment which proves to be unfavorable to some breast cancers; otherwise the incidence would not drop sharply during this period.

Stewart also noted that occasionally papillary lesions of the breast may show definite involutional changes, with atrophy and fibrosis. At some point in the regression, it is impossible to tell whether the cells are cancerous or not. Under these circumstances, Stewart believes that small early breast cancers may disappear spontaneously, *i.e.*, because of spontaneous alteration in the hormonal environment.

EFFECTS OF THERAPY

Cancer of the breast

The best method of treatment for cancer of the breast at the present time is *radical surgery*, with careful dissection of the adjacent lymph nodes. In addition, irradiation has been used postoperatively, in order to prevent a possible recurrence and in the treatment of manifest metastases. Although *irradiation* is valuable for palliative relief, there is no convincing proof as yet that life can be prolonged. Manipulation of the hormonal environment of the patient is another way in which the growth of cancer of the breast can be influenced. The available methods of manipulation are excision or irradiation of the ovaries, administration of androgens, treatment with estrogenic substances (under certain conditions), therapy with other steroids such as cortisone, and adrenalectomy.

* F.A.C.A.

It had been known for years that women with cancer of the breast who become pregnant invariably fare very poorly. It had likewise long been known that advanced breast cancer has sometimes regressed in women who were spontaneously castrated as a result of ovarian metastases. These observations prompted Beatson (3) to attempt *surgical castration* for mammary cancer. His experiments, and those of others, showed that although the cancers regressed for a short time after surgical castration and there was some subjective improvement, practically all the patients followed the usual downhill course. Benefits sometimes obtained are relief of pain, diminution of the primary tumor, or healing of ulcers, but these effects are transient in most cases, lasting only six to twelve months.

Similarly, *roentgen irradiation of the ovaries* and of tumor metastases sometimes can cause remarkable relief of pain, general improvement in health and some regression of bone metastases—always of a transient nature. Bone metastases respond best, but irradiation does not prevent new lesions from appearing. In most of the patients cited in the literature, both the ovaries and metastases were irradiated, but in the few series in which only the ovaries were treated, significant temporary alleviation occurred (4).

In 1939, Loeser (5) used *testosterone* in the treatment of 2 women who had functional uterine bleeding. He observed that in these women, who had also had carcinoma of the breast, there were no recurrences during the period of therapy with testosterone. Ulrich (6) made the same observations simultaneously. Farrow and Woodward (7) observed some benefit in a small series. Adair (8) continued the experiment with a dosage of 25 mg. of testosterone propionate daily over extended periods; in an occasional patient, the relief of pain appeared to be striking.

The effects of testosterone therapy of advanced breast cancer, although temporary, are sometimes remarkably salutary, *e.g.*, gain in weight, decreased pain, and decreased need for narcotics (9). Some of the improvement may be due to the general anabolic effects of the steroid. Osseous metastases are often benefited. On the other hand it is well known that the dosages required for relief may precipitate distressing symptoms of masculinization and salt and water retention.

In 1950 Nathanson (10) reported benefit, similar to that obtained from testosterone, in a group of postmenopausal women treated with *estrogens*. The mode of action of this substance is entirely unknown. Haddow *et al.* (11) had previously shown that many carcinogenic hydrocarbons had the property of retarding growth of malignant tissues, and they observed a retardation of growth of cancer of the breast in some instances following treatment with estrogenic substances. Improvement in some cases may be as spectacular as with testosterone, namely, increase in weight and appetite, and occasional regression of bone, lung and cutaneous lesions. Most authors have warned against giving estrogens to women before the menopause, because of possible acceleration of the course of the cancer. Such acceleration is not, however, invariably the case. Side effects from estrogens are frequent, including edema, vaginal bleeding,

pigmentation of the areolae of the nipples and hypercalcemia. Some forms of estrogen may cause nausea and vomiting early in the course of therapy; this effect may sometimes be abolished by changing to another form of estrogen.

Methyl androstenediol has been used because of a metabolic similarity to testosterone (12). Although it causes less masculinization, it also causes less satisfactory improvement.

Another compound, *androstanolone* (Neodrol), is at least as effective as testosterone, but has considerably less androgenicity (13). Although it inhibits the progression of carcinomatous lesions and causes some regression of the lesions for various lengths of time, the degree of hirsutism and change in the voice is relatively mild. Eventually, the carcinoma escapes hormonal control.

The adrenal gland produces steroids, both estrogenic and androgenic, and it is therefore probable that hormone-dependent breast cancers receive support from this source after the ovaries are removed. On this basis, it was logical to observe the effect of *adrenalectomy* in bringing about additional improvement in cases of hopeless breast cancer, by removing another source of estrogens. Pearson *et al.* (14) reported observations on 10 patients who had undergone adrenalectomy. Four patients had previously failed to respond to castration; none responded to adrenalectomy. In 6 who had objective improvement following castration, 3 responded to adrenalectomy, and in 2 additional patients some alteration in tumor growth was observed. Apparently only estrogen-dependent cancers respond, which is in itself a logical assumption. Subjective and objective improvement occur, but are of a temporary nature.

Following adrenalectomy, it was necessary to supply cortisone in order to keep the patients alive. When, in addition, there was satisfactory progress with cortisone support, it was natural to think that *cortisone* itself might be of value. Pearson (14) found some benefit with doses of 200 mg. daily. The series consisted of 3 patients who had been surgically castrated without benefit. They all had osteolytic metastases and marked hypercalcuria and hypercalcemia. Administration of cortisone was followed by prompt clinical improvement and satisfactory pain relief; this relief coincided with a decrease of the blood calcium level and a decrease of the urinary calcium excretion to normal values. However, cortisone-induced improvement is also of a temporary nature.

Luft and Olivecrona (15) performed *hypophysectomy* on 9 patients with far advanced carcinoma of the breast who had recurrences after mastectomy, and widespread metastases. Although the follow-up period following hypophysectomy was short, the authors stated that the operation was well tolerated, but that unless hypophysectomy was complete, there was only a temporary effect of short duration. They describe a 49-year-old patient who had a satisfactory operation, resulting in a remarkable regression of the carcinoma. However, the improvement following hypophysectomy is of a temporary nature.

Cancer of the prostate

The only other type of cancer that has been conclusively proved to be hormone-dependent is carcinoma of the prostate. Stewart (2) believes that spon-

taneous alteration of the hormonal environment may explain some cases of long evolution of prostatic cancer, and be the reason why many latent cancers of the prostate never reach fruition during the patient's lifetime. In some cases of untreated latent cancer of the prostate Stewart also observed microscopic effects that he had seen in other patients who were given estrogens.

The only cure for prostatic carcinoma is *radical surgery* undertaken before the lesion has extended beyond the prostatic capsule. When prostatic cancer has spread beyond the immediate boundaries of the gland, the surgeon is concerned with two objectives: 1) relief of urinary symptoms by transurethral resection, and 2) retardation of the growth of the tumor and its metastases.

Hormonal treatment of prostatic carcinoma is based on the fact that androgen stimulates prostatic development, and estrogens inhibit or neutralize the stimulus of the androgens (36). Therapy aimed at androgen control includes orchiectomy, estrogen administration, adrenalectomy, cortisone administration and hypophysectomy. Histologic changes in the prostatic tumor cells are greater following *estrogen administration* than following orchiectomy, but *orchiectomy* may produce better clinical results. Orchiectomy and estrogen therapy used together or successively improve up to 90 per cent of inoperable patients, and approximately 75 per cent live comfortably for five years (17).

Bilateral adrenalectomy has been tried after the effects of orchiectomy and estrogen therapy have been dissipated, on the basis of eliminating another source of androgen. Some patients have been given a further degree of comfort by this operation, but it has not caused metastatic lesions to disappear and new lesions may develop. Cortisone administration must be used as supportive therapy following adrenalectomy, and this drug may also contribute a share of its own to the improvement of these patients.

Whitmore and his colleagues (18) reported on 17 patients who were subjected to bilateral adrenalectomy for advanced prostatic cancer. Of 15 patients who survived longer than one week postoperatively, 11 had a short subjective remission, but in only 6 of these 11 did the improvement last more than two months. Objective improvement was observed in only 2 patients. In no instance was there a drop in the acid-phosphatase level as a result of bilateral adrenalectomy. It may, therefore, be concluded that it is unwise to submit patients to this ordeal for such meager rewards.

Luft and Olivecrona (15) performed *hypophysectomy* on 1 patient with carcinoma of the prostate gland. Difficulty of urination disappeared after an incomplete hypophysectomy. Relief of pain lasted until death, which occurred four months after the operation.

We still do not know the basic cellular mechanisms that account for the dependence of the prostatic epithelium upon androgens. When these are known, new therapeutic approaches may be introduced.

COMMENT

The final results of alteration of the hormonal environment in patients with carcinoma of the breast or prostate can not be considered as spectacular. How-

ever, these studies must be viewed as clinical experiments. If the results are treated in this light, it may be stated that in some cancers growth is not entirely autonomous, and is partly dependent on certain known substances. Undoubtedly many factors are involved, but some knowledge of even one of these is a significant gain.

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THE ACTION OF 267C (1-(1-PIPERIDYL)-6-METHYL-3-PHENYL-3-HEPTANOL HYDROCHLORIDE) IN PARKINSON'S DISEASE

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At a meeting of the New York Neurological Society some years ago, the late Dr. Foster Kennedy, after hearing great claims made for the effectiveness of a new drug in the treatment of Parkinson's disease, rose to state that he had heard such claims before, but that a clinic full of parkinsonian patients still looked essentially the same as a clinic full of parkinsonian patients in prior decades. Unfortunately, this observation still holds true in the main, although new drugs continue to be reported with enthusiasm and surgical "cures" are announced with great fanfare. Nevertheless, if one becomes discouraged with what has been accomplished up to now, it is easy to regain one's courage by withdrawing medication and observing the devastating effects of just such a simple maneuver.

In the present investigation, a new drug, designated by Lederle Laboratories as compound 267C, has been studied for its influence upon parkinsonism. Compound 267C, which bears the chemical formula 1-(1-piperidyl)-6-methyl-3-phenyl-3-heptanol hydrochloride[1], is closely related in structure to Artane (trihexyphenidyl) and Pagitane (cycrimine hydrochloride). Pharmacologic studies (1) indicate that its principal action is antispasmodic. It has far less mydriatic effect than Artane, has but one-fiftieth the antisialogogue action of atropine, one-fiftieth of the inhibitory action of atropine on the cardiac vagus, and a mild antihistaminic effect. Central nervous system excitement with compound 267C is less than that with Artane and less by far than that with atropine. Thus, compound 267C appears to possess certain favorable atropine effects with fewer of atropine's "side reactions." Toxicity studies in animals (1) and in human beings (2) have revealed no significant unfavorable effects from doses several times the average therapeutic dose.

MATERIALS AND METHODS

Thirty patients were studied, of whom 9 were women and 21 men. Their ages ranged between 45 and 75 years. They had been ill with Parkinson's disease for periods of from two to twenty-four years. All patients had taken various combinations of drugs for months or years, including Artane, various solanaceous compounds and various antihistaminics. The patients were studied for periods which varied from eleven days to four and a half months. In 19 cases, complete blood counts and urinalyses were performed prior to, and at the completion of the observation period.

[1] Generous supplies of this material were furnished to us by Lederle Laboratories, Pearl River, N. Y.

TABLE 1. *Summary of Effects of 267C in Patients with Parkinson's Disease*

Patient	Age	Sex	Treatment with 267 C: Daily dose (mg.)	Treatment with 267 C: Duration (days)	Clinical Manifestations*: Rigidity Before	Rigidity After	Tremor Before	Tremor After	Gait Before	Gait After	Salivation Before	Salivation After	Mental attitude Before	Mental attitude After	Overall Improvement†	Side Effects	Comparison with Other Treatment	Comments
G-1	50	M	15		3	3	2	2	3	3	0	0	2	0		None	Equiv. to 2 mg. Artane t.i.d. + ½ tab. Rabelon q.i.d.	When given placebo after 267C, slowness of motion, lethargy and rigidity increased after 5 days.
			20	16	3	2	2	1	3	2	0	0	2	1	Slight	None		
			30		2	2	1	1	2	2	0	0	1	1		None		
G-2	66	M	15		2	2	1	1	1	1	0	0	1	1		None		No withdrawal symptoms noted when Artane, belladonna or 267C discontinued.
			30	16	2	1	1	1	1	1	0	0	1	1	Slight	None		
			40		1	1	1	1	1	1	0	0	1	1		None		
G-3	69	M	7.5	7											None	None	Equiv. to 2 mg. Artane t.i.d. + 2 tab. Rabelon daily	Patient went downhill after improvement for 1 month. Downward course continued after change to Artane. Patient finally died.
			20	7											None	None		
			20-Rab	54											Slight, for 1 mo.	None		
G-4	45	M	20	10	4	4	2	2	3	3	2	1	2	1	Slight	None		When given placebo after 267C, noted slight withdrawal symptoms.
			30	6	4	3	2	2	3	3	1	1	1	1	Slight	None		
G-5	72	M	15	6	4	4	0	0	4	4	1	1	2	2		None		No withdrawal symptoms when Artane or 267C discontinued.
			30	10	4	4	0	0	4	4	1	1	2	2	None	None		
G-6	68	M	20	10	4	4	2	2	3	3	3	1	2	1		None		When placebo was given after 267C, withdrawal symptoms were noted.
			30	6	4	3	2	2	3	3	1	1	1	1	Slight	None		
G-7	65	F	20	62		Impr.‡		Impr.‡		Impr.‡				Impr.‡	Slight	None		When placebo was given instead of 267C, withdrawal symptoms were noted.
G-8	65	M	7.5	2												None		
			15	7												None		
			30	7											None	None		
G-9	53	M	7.5													None		
			15	11												None		
			20												Slight	None		
G-10	64	M	15	5	4	4	3	2	4	2	0	0	0	0	Slight	None		
B-10	53	M	15	147											Slight	None		
			30												Slight	Drowsiness and nervousness	Better than atropine	
M-1	69	M	15	42	4	2	4	0	4	1	3	0	3	1	Marked	None	As good as Artane; better than belladonna, hyoscine & Pro-dol	

B-10	53	M	15 30	147											Slight	Drowsiness and nervousness	Better than atropine	
M-1	69	M	15	42	4	2	4	0	4	1	3	0	3	1	Marked	None	As good as Artane; better than belladonna, hyoscine & Benadryl	
M-2	61	M	15 20	14 35	2	1	4	1	1	1	1	0	1	1	Slight	None None	Not as good as Artane	
M-3	58	F	15 20	14 56	4	4	4	2	3	2	4	3	4	2	Slight	None Blurred vision	Better than hyoscine; not as good as hyoscine plus Benadryl	The blurred vision occurred in the morning.
M-4	64	M	20	105	4	1	4	0	4	1	2	0	4	2	Marked	Dryness of mouth	As good as Artane or Artane plus Benadryl; better than belladonna	The dryness of the mouth occurred only occasionally.
J-1	75	F	15–25	126	3	2	3	2	2	1	2	0	3	2	Marked	Transitory headache	As effective as atropine, 1/150 t.i.d.	Headache disappeared with continued medication.
J-2	73	F	15–35	91	2	2	2	2	2	2	1	1	1	1	None	Dizziness	Artane not effective either	Dizziness occurred when given 35 mg. daily.
J-3	57	F	15–20	91	3	3	2	2	3	2	1	1	3	1	Slight	None	Better than hyoscine, gr. 1/100 daily	
J-4	67	M	15–25	35	4	2	3	2	4	2	3	2	2	2	Slight	None	Not as good as Artane in control of salivation	
J-5	69	M	15–25	35	3	2	3	2	4	1	3	2	3	0	Marked	None	Not as good as Artane in control of salivation	
J-6	57	F	15–20	14	3	3	3	3	3	3	2	2	2	2	None	Nausea; headache	Not as good as Artane	
J-7	58	F	15	7	3	2	3	2	3	0	2	1	2	1	Marked	None	As effective as Artane	
J-8	56	M	15–35	52	2	2	3	3	2	2	0	0	2	2	None	Headache; dizziness	Hyoscine not effective either	Side effects appeared on 35 mg. per day.
J-9	59	M	20	7	3	3	2	2	3	3	1	1	3	3	None	None	Not as good as Artane	
J-10	61	F	15–20	21	3	2	3	3	3	2	3	3	2	1	Slight	None	Not as good as Artane in control of salivation	
J-11	56	F	15	7	3	1	3	2	3	1	3	2	2	0	Marked	None	Not as good as Artane in control of salivation	
J 12	64	M	15–20	14	3	1	1	0	2	1	2	1	2	0	Marked	None	Not as good as Artane in control of salivation	
J-13	58	M	15–25	35	3	3	2	2	2	2	0	0	1	1	None	None	Not as good as Artane	
J-14	62	F	15	42	2	1	3	1	1	0	2	1	2	1	Marked	Transitory nausea	As good as hyoscine	Nausea disappeared with continued medication.
J-15	49	M	15–20	49	2	1	2	2	2	2	2	2	3	1	Slight	None	Better than Artane	

* Gradation of clinical manifestations:
0 = Not present, or minimal residuum.
1 = Slight, causing no disability.
2 = Moderate, interfering with activity only slightly.
3 = Marked; activity curtailed in major degree, but not incapacitated.
4 = Patient incapacitated, sometimes bedridden.

† Improvement:
None = No change.
Slight = One or more manifestations slightly improved.
Marked = Considerable improvement in one or more manifestations.

‡ Improvement noted by physician, although symptoms not graded.

RESULTS

So great are the spontaneous day-to-day variations in the degree of dysfunction in parkinsonian patients that there was a time when parkinsonism was considered to be a functional disorder. Accordingly, in the present series of cases, the usual difficulties in evaluating the results of therapy were encountered. There is as yet no mechanical device by which we may measure the effects of therapy. Emotional factors discount the reliability of such measurements as dexterity tests or the speed of walking a measured distance. Electromyography is of little value in measuring changes induced by drugs (4). Unfortunately, therefore, one must rely on clinical evaluations, which admittedly lack the objective character of a change in blood pressure or a fall in temperature. Nevertheless, frequent observations of the patients, reports from nurses or from relatives and, most important, lack of preconceived notions on the part of the observer, allow one to make reasonably reliable evaluations of significant changes.

Nine patients showed striking subjective or objective regression while receiving placebos, whether the placebos were given at the beginning of the observation period or substituted later for actual medication. These subjects complained of weakness and stiffness and increased difficulty in walking and in feeding themselves. Indeed, some were no longer able to walk, and remained in bed. In others, the increase in rigidity and sialorrhea was unquestionably beyond the range of normal daily variation. This placebo effect was routinely apparent after two to four days.

Eight patients showed marked improvement, 15 patients showed slight improvement and 7 showed no improvement during therapy with 267C. The effective dose was one or two tablets given three times daily. Side effects were observed in 8 cases. The details are listed in Table 1.

When the effects of 267C were compared with the effects of previous medications, it was found that 267C was better in some cases than atropine, belladonna or hyoscine, but often less useful than any of these and rarely as helpful as trihexyphenidyl (Artane).

SUMMARY

1. Nine women and 21 men with Parkinson's disease were given 267C (1-(1-piperidyl)-6-methyl-3-phenyl-3-heptanol hydrochloride).

2. Marked improvement was noted in 8 patients, slight improvement in 15, and no improvement in 7.

3. Side effects were observed in 8 patients.

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THE MENOPAUSE AND MYOCARDIAL INFARCTION

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For some years it has been recognized that an impressively smaller number of women who have not yet undergone the menopause suffer attacks of myocardial infarction than do men of comparable age. In fact, in the absence of a complicating associated disease, such as hypertension or diabetes mellitus, myocardial infarction is rare in women of premenopausal age. Logically, something must happen to women at the time of the menopause which makes them much more susceptible to myocardial infarction; this may be some process either inherent in the menopause or associated with it only by coincidence.

Recently, we conducted a study of myocardial infarction in women in the hope of shedding some light on the nature of the "immunity" to this disease that women of premenopausal age seem to enjoy (1). The records of 146 consecutive women with myocardial infarction admitted to the Henry Ford Hospital from July 1949 to July 1953 were reviewed. The basis for the clinical diagnosis of myocardial infarction was a typical series of electrocardiograms, associated with compatible clinical manifestations and at least one of the following: fever, leukocytosis with or without neutrophilia, and an elevated erythrocytic sedimentation rate. A diagnosis on any other basis was accepted only if proved by autopsy.

RESULTS

General

The youngest and the oldest patient in this series were 27 and 81 years of age, respectively; the average age at which the initial infarct occurred was 64 years. There was a remarkable preponderance of women who were in the sixth through eighth decades of life. Studied by five-year periods, this series showed a sharp upswing in the incidence of infarction after the age of 45 years (Table 1).

Menopausal and menstrual data

Eleven women were still menstruating at the time of their initial attack of infarction. In 27, the age of the patient when the menopause occurred was not recorded, although the age at which all 27 had their initial attack of infarction was considerably later than the age generally accepted for the occurrence of the menopause. The average age of the 108 patients in whom the date of the menopause was recorded was 47.4 years. Thus, the interval between average time of the menopause and the time of the initial attack of infarction was 16.6 years.

Other menstrual data were available in some of the women. In 61 patients

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TABLE 1

Distribution of 145 Women with Myocardial Infarction According to Age Groups*

Age Group (yrs.)	No. of Patients
20–29	2
30–39	3
40–44	2
45–49	10
50–54	17
55–59	26
60–69	55
70–79	27
80–89	3
Total	145

* In 1 woman among the total of 146, the exact age at the time of infarction was uncertain.

the menarche occurred at slightly over 14 years of age. The menstrual cycle was described in 43 women: 39 had regular periods of normal duration and amount, 1 had regular periods with scant flow, 2 had irregular periods, and 1 had irregular periods plus spontaneous amenorrhea of ten years' duration. The number of pregnancies was recorded in 88 women and averaged 3.4 per patient. The number of deliveries in 122 women averaged 2.6 per patient.

Thirty-six patients had had pelvic operations. Only 2 women had had bilateral oophorectomy prior to the menopause, their operations being at the ages of 40 and 42 years; their initial infarctions occurred at the ages of 67 and 58 years, respectively.

Incidences of hypertension and diabetes

The incidences of hypertension and diabetes were high in all age groups. These two diseases were present, alone or in combination, in 69.9 per cent of all patients. A slightly smaller percentage was afflicted by one or both diseases among those still living than among those who died (64.8 per cent and 77.6 per cent, respectively). The level above which blood pressure was considered hypertensive was 160/100 mm. Hg.

Incidence of obesity

Weight was recorded in 130 patients. Patients weighing more than the maximum amount listed for the given height of a large-framed person in standard life insurance tables were considered obese. Eighty-four (64.6 per cent) of the 130 were obese. The percentage of obesity among the patients who died (60.4 per cent, or 29 of the 58 fatal cases in which weights were recorded) was approximately the same as that among the living (67.1 per cent, or 55 of the 82 who were weighed).

Causes of death

At the time of the study, 58 of the 146 women were dead; autopsy had been performed in 32 (55.2 per cent) of these. Thirty-six patients died within the first year after their attack of infarction, 7 within two years and 8 within three years. The longest survival of those who are now dead was ten years. The number who died within the first year after the initial attack progressively increased with each decade, *e. g.*, in the seventh decade, 16 of the 20 dead at the time of this study expired within the first year after the initial infarction. To obviate inappropriate implications, it should be borne in mind that most of the patients in this study are still living.

The causes of death in these 58 women were cardiac in 45 (77.6 per cent), non-cardiac in 8 (13.8 per cent), and unknown in 5 (8.6 per cent). Of the cardiac deaths, 28 occurred within the acute phase (first month) of the initial infarction, 12 within the acute phase of a subsequent infarction, and 5 from other cardiac causes (*i.e.*, without evidence of fresh infarction). Thus, 40 of the 58 dead at the time of this study had died in the acute phase of myocardial infarction, and in 28 of these the attack was the initial one. Of the 8 non-cardiac deaths, 4 were due to cerebrovascular accidents, 2 to mesenteric thrombosis, 1 to Hodgkin's disease, and 1 to suicide.

Pilot angina

A specific history of the presence or absence of angina pectoris preceding the initial infarction was recorded in 119 patients. Of these, 48 (40.3 per cent) had no pilot angina. Among the 71 (59.7 per cent) who did have this warning, 16 had had pain for less than two months, 8 for two to six months, 9 for six to twelve months, and 24 for over a year (a range of fourteen to ninety-six months, the average being forty-seven months). Fourteen women had had definite angina prior to infarction, but were unable to say for how long. No patient having an initial infarction after the menopause had angina prior to the menopause.

Hematologic observations

The white and red blood cell counts, and the erythrocytic sedimentation rate were not different from those reported by others (2, 3). The hematocrit (Wintrobe) averaged 45 mm. in 115 patients, a level slightly higher than the average for menstruating women; but most patients in this series had already undergone the menopause. One patient showed a positive serologic reaction for syphilis but no clinical evidence of syphilitic cardiovascular involvement.

Premenopausal group

Since myocardial infarction in women of premenopausal age is uncommon, the women who had not yet undergone the menopause deserve some description. Three began to have menopausal symptoms within one year after the infarction; 2 of these were 47 years old and 1 was 50 years old at the time of occur-

rence of the initial infarct. The ages of the other 8 were 27, 33, 34, 36, 41, 44, 45 and 45 years. The youngest had a systemic vascular disease which defied specific diagnosis despite intensive study. Of the 3 women in the fourth decade of life, the one who was 33 years old had severe chronic hypertension (average, 230/150 mm. Hg), the one who was 34 years old had a probable coronary embolus from rheumatic mitral valvulitis, and the one who was 36 years old had severe diabetes mellitus and at autopsy was found to have intercapillary glomerulosclerosis and nephrosis in addition to acute myocardial infarction. Seven of the 11 women were older than 40 years; 1 of these had polycythemia rubra vera, and 5 had either hypertension, diabetes, or a combination of the two. Thus, only 1 of these patients had no recognizable systemic disease which could affect coagulation or blood vessel structure; this woman was 47 years old and slightly obese. She began having menopausal symptoms less than one year following infarction.

DISCUSSION

The preceding observations evoke a number of considerations. Paramount among these is that myocardial infarction in women of premenopausal age is indeed a rare phenomenon. Furthermore, this disease is even rarer in women of premenopausal age without diabetes mellitus, hypertension or systemic disease affecting coagulation or blood vessel structure. This is in striking contrast to men of comparable age, in whom myocardial infarction due to spontaneous atherosclerosis is not at all uncommon.

An important corollary is the sharp increase in incidence of myocardial infarction in women who have undergone the menopause. If these two points are approached conversely, an understanding of the reason for the increase in this incidence should explain why women of premenopausal age enjoy protection from myocardial infarction.

One point which contributes some confusion to this problem is the frequent synonymous use of the terms myocardial infarction and coronary atherosclerosis. Although most attacks of myocardial infarction are due to coronary atherosclerosis, it is fallacious to employ the two terms interchangeably. For example, although 55 per cent of the women in one series (4) had severe coronary sclerosis, only 6 per cent had clinical evidence of coronary disease. If the distinction between these two terms is understood, study of the relationship between them and the menopause may be more accurately conducted.

One obvious change at the time of the menopause is cessation of production of estrogen. Evidence has been presented, both in humans and in experimental animals, that estrogens affect cholesterol metabolism and thereby atherosclerosis (5–9). Utilizing this information, Wuest, Dry and Edwards (4) carefully examined the coronary arteries of bilaterally oophorectomized women and found a greater amount of atherosclerosis in them than in the arteries of a control group. Barr (5) was able to lower the cholesterol/phospholipid ratio in male survivors of myocardial infarction who volunteered to try estrogens.

Although the anti-atherosclerotic effect of estrogen has received wide atten-

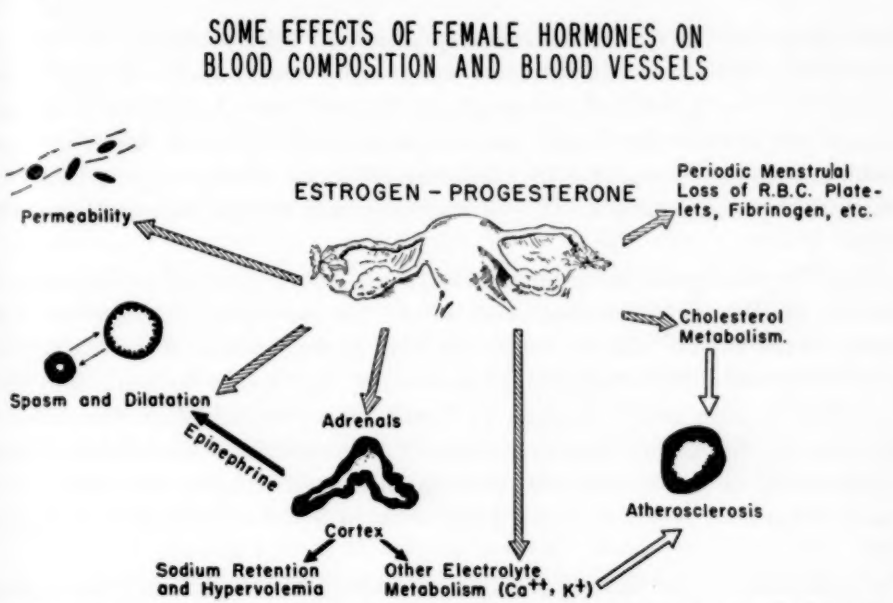

FIG. 1. A schematic representation of the effect on blood composition and blood vessels of the hormones of a woman in the reproductive phase of life. (Courtesy of *Ann. Int. Med* **43:** 153 (July) 1955.)

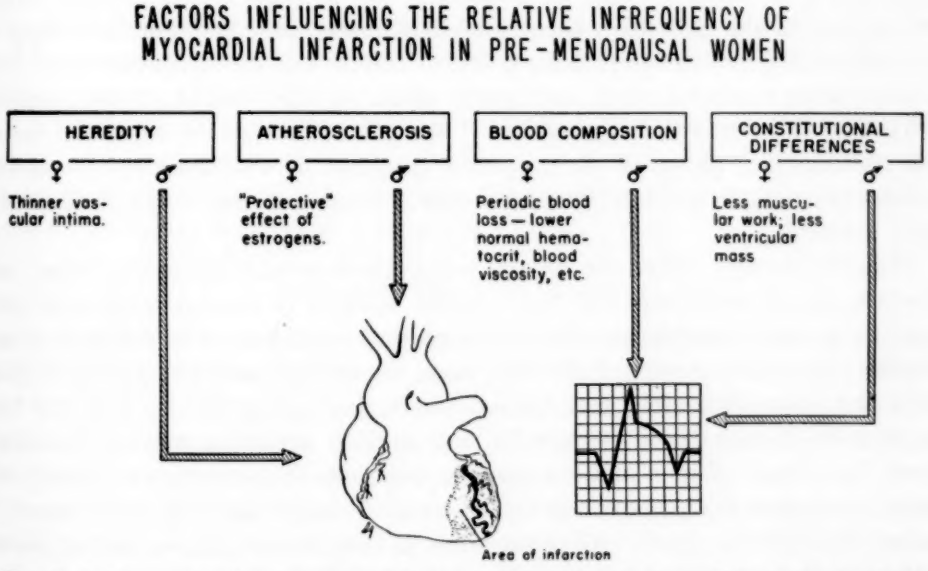

FIG. 2. A diagrammatic summary of factors influencing the sexual disparity in the incidence of myocardial infarction before middle age (Courtesy of *Ann. Int. Med.* **43:** 153 (July) 1955.)

tion, estrogen also has other effects on the blood and blood vessels (Fig. 1). In addition, there are certain congenital and constitutional factors which are pertinent to the sexual disparity in the incidence of myocardial infarction before middle age (Fig. 2).

Estrogens may affect cholesterol deposition in atherosclerosis by way of an intermediary effect on calcium and magnesium metabolism. Recent evidence reported by two groups of investigators support this possibility. Uhl and associates (10) found they could alter experimentally induced atherosclerosis in rabbits by using Versene for its chelating effect on calcium and possibly magnesium. Perry and Schroeder (11) obtained similar results, using other chelating agents.

Action by estrogens on other electrolytes, either directly or because of an influence on the adrenal cortex, also affects the cardiovascular system. For example, premenstrual sodium retention and hypervolemia periodically distend the blood vessels. Premenstrual edema is not due solely to sodium retention, since there is also some increase in capillary permeability at this time (12). Alteration in the sensitivity of capillaries to epinephrine and consistent arteriolar dilatation in the bulbar conjunctiva of women during the week prior to menstruation has recently been demonstrated by Landesman and associates (13).

In addition to the hormonal changes during menstruation, the menstrual blood loss itself has a direct effect on the blood composition of women in the reproductive phase of life. The average concentration of various constituents of blood is less than that of men of comparable age, the relative red blood cell mass being a notable example. Following the menopause, the relative blood cell masses of the two sexes become similar. Some have thought that there are periodic alterations in the platelet count at the time of menstruation (14). There is also some evidence of an estrogenic effect on the control of hematopoiesis (15). The difference in composition of the blood between women and men in the reproductive phase of life raises the question of whether there is an analogous difference in the facility with which a thrombus may occur in their coronary arteries.

Constitutionally, there are several self-evident sexual differences which offer the woman of premenopausal age a lesser amount of cardiac work and which may have some bearing on the infrequency of infarction. Her heart is usually smaller than that of men of the same age, requiring a smaller amount of blood from the coronary vessels. Her body is smaller, requiring less work by the heart to provide it with blood. Generally, her routine activities involve less heavy work than those of men of the same age (whereas the activities of women who have undergone the menopause and of men of similar age are more nearly the same). And finally, Dock (16) demonstrated that female infants have a thinner intima in their coronary arteries than have male infants.

Study of the menstrual cycles, number of pregnancies per woman, and similar related data showed no preponderance of hypoestrogenic or masculinized females in this series. Since most of these patients had already undergone the menopause, however, one might classify them as hypo-estrogenic in a physiologic sense. It is of considerable interest that the 11 women who had their initial attack of infarction prior to the menopause were all menstruating regularly, at least until the time of the attack.

As has been suggested by others (2, 17–19), most women in whom myocardial infarction develops have either hypertension, diabetes, or both. Perhaps of even more diagnostic significance, however, is the implication from this study that virtually all women of premenopausal age who have myocardial infarction will also have singly or in combination the following maladies: hypertension, diabetes, systemic diseases involving alteration of the clotting mechanism (*e.g.*, polycythemia rubra vera) or integrity of blood vessels (*e.g.*, polyarteritis nodosa). In brief, substernal pain in women of premenopausal age with one of these diseases must be viewed with a much higher degree of cardiac suspicion.

Of undetermined significance is the fact that over 60 per cent of the women in this series were obese; the weight range of a similar group of women in the postmenopausal age without myocardial infarction would lend value to this observation. Obesity provided little prognostic significance once the infarction had occurred, since the incidence of obesity among those still living was approximately the same as among those who died.

The evidence obtained from these observations seems to favor the opinion that the menopause is more than coincidentally involved in the sharp increase of myocardial infarctions in women after the menopause. Since the degree of coronary atherosclerosis in women apparently follows a gradually progressive increase from the ages of 30 to 75 years (20), one could presume that the loss of anti-atherosclerotic protection of estrogens (if there be such a phenomenon in humans) is not the only, and perhaps not even the major change incurred at the menopause to render these women more susceptible to myocardial infarction.

At the age of 64 years (average age of initial infarction in our series) the average degree of coronary atherosclerosis in women is significantly less than in men of the same age (20, 21), whereas the incidence of myocardial infarction in the two sexes at this age is similar (22).

SUMMARY AND CONCLUSIONS

1. Study of 146 women with myocardial infarction revealed a sharp increase in the incidence of that disease in those who had undergone the menopause.

2. Ten of the 11 women who had not yet undergone the menopause had some disease which affected either coagulation or integrity of the blood vessels, such as hypertension, diabetes or polycythemia vera.

3. Although more discussion is accorded to the effect of estrogens on cholesterol metabolism and experimental atherosclerosis, estrogens have other important effects on blood vessels and their contents, such as influencing vascular tone, electrolyte metabolism and constitutional development

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MORBIDITY AND MORTALITY IN OLD AGE.

A Study of Experience in a Modern Home for the Aged. Part III*

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METHODS OF STUDY AND BASIC DATA

Population

The population figures used in this study are based on information provided by the records of the Home for Aged and Infirm Hebrews of New York. All material bearing on such matters as national origin, citizenship, and length of residence in the United States of the residents of the Home was derived from the records of its Social Service Department. These data are to be found in the preceding section of this study. The remaining data were derived from the records of the Medical and Psychiatric Departments.

The population of the Home is fluid. There are permanent withdrawals (residents leave of their own volition, or may be sent to Bellevue Psychiatric Division); there are temporary withdrawals (residents may leave for vacation or may be sent to nearby hospitals for indicated surgery); there are new entrants; and there are deaths among the residents. The census of two different departments at the Home may vary widely at any given time. For example, if on May 1 there are 20 residents on temporary leave, the Medical Department census will show 20 fewer people present in the Home, whereas the Social Service census will not deduct these 20 people from the total population.

Cause of rejection of applicants to the Home

From the closed records of the Social Service Department of the Home, data on causes of rejection were obtained and entered in a master table. The following items were included: name, sex, year of rejection, cause of rejection, age on rejection, nativity, and length of stay in the United States prior to being rejected. The information obtained from the completed table made possible the construction of two other tables (Nos. 16 and 17 in Part II, *J. Am. Geriatrics Soc.* July 1956) showing the causes of rejection and the sex and nativity of the rejected applicants during the total period of this study.

The observed percentage difference between the rejection rates for male and female applicants was tested for statistical significance in the following manner.

* Part of thesis presented to the Faculty of the Department of Public Health, Yale University, for the degree of Doctor of Public Health, 1955. (Parts I and II appeared in the June and July issues of this journal.) This study was carried out under the auspices of the Medical Services of the Home for Aged and Infirm Hebrews of New York.

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The standard error of the difference was obtained, using the formula:

$$\text{S.E.}_{\text{diff}} = \sqrt{\text{S.E.}_{p_1}^2 + \text{S.E.}_{p_2}^2}$$

$$\text{S.E.}_{p_1} = \sqrt{\frac{p_0 q_0}{n_1}}$$

$$\text{S.E.}_{p_2} = \sqrt{\frac{p_0 q_0}{n_2}}$$

where p = observed percentage
p_0 = the overall percentage
q_0 = 100 per cent − p_0
n = sample size
Numerical subscripts identify the two different samples.

The observed percentage difference was then divided by the standard error of the difference, to obtain the relative deviate[1] (Dev./σ), in standard deviational units.[2]

Method of obtaining the population of the Home

The population base for determining mortality and morbidity was not established by using the "official" numbers of residents, but by a consideration of entries and withdrawals. Inasmuch as all those present on January 1, 1935 and all entrants since then were known by name and by year of entry (in over half, by month as well as by year of entry), and inasmuch as the exact day of death or withdrawal for other causes was known, this information was used to arrive at a more precise census.

In order to obtain the basic population data, two master tables were constructed: one for the entrants to the Home for Aged and Infirm Hebrews, 1935–1951; the other for the population residing in the Home on January 1, 1935. The following items were included in each master table: name, sex, year admitted, age on admission, date of death or withdrawal alive, and age at death or withdrawal alive. The information obtained from the completed tables made it possible to construct two tables (Nos. 7 and 8 in Part II, *J. Am. Geriatrics Soc.* July 1956) showing the population of the Home for Aged and Infirm Hebrews during the total period of this study and also for the three time periods.

Time periods

The seventeen-year interval studied was divided into three almost equal time periods—six years, five years, and six years. It was noted that: 1) The time period 1935–1940 saw the introduction of the sulfonamides, and was also the period in which the Home did not have an infirmary in which complete hospital care could be given. 2) During the five-year period 1941–1945, the Home acquired (in 1942) a modern infirmary, completely equipped to meet

[1] *See* Table 18, in Part II (*J. Am. Geriatrics Soc.* July 1956).

[2] Relative deviates of 2.58 or more (P, 1 per cent or less) were considered significant in all tests of the percentage difference between two samples.

most diagnostic and therapeutic needs; these years also witnessed the introduction of penicillin. 3) In the six-year period 1946–1951, penicillin and the other antibotics became generally available.

Morbidity

Functional classification

A survey, designed to enumerate and classify the various diseases met with at the Home, was started and completed during the fall of 1953. This survey included only those residents living in Central House and the Apartment Projects. At this time, the total population of these units was 498 (Table 19).

It was found that the population of the Home was divided for administrative purposes into the five following groups on the basis of functional capacity:

Class A. Individuals capable of unlimited and unsuppressed activity, who may be trusted to go about the street in safety.

Class B. Individuals capable of moderate activity, to be trusted in the neighborhood of the Home, but who may need the escort of a younger person for extended or tiring trips.

Class C. Individuals whose capabilities are limited and whose activities need both assistance and supervision; they are practically housebound and require escort on the street.

Class D. Individuals who are confined to bed or its immediate vicinity.

Class E. Individuals who are totally blind, or whose vision is so impaired that they must be specially instructed in taking care of themselves.

Classes A and B embrace relatively self-sufficient individuals, whereas the remaining categories are made up of the severely handicapped. Comparisons were made between these two groups, which were called the non-nursing-home and the nursing-home groups, respectively.

TABLE 19

Number of Residents in Home for Aged and Infirm Hebrews (W. 105th St. and Apartments) According to Functional Classification as of November 1, 1953

Category*	Male	Female	Total
A (apartments)	47	118	165
B (rooms)	76	99	175
C (dormitories)	36	74	110
D and E (infirmaries)†	17	31	48
Total	176	322	498

* A. Ablebodied—apartment project or room.
B. Partially disabled—room.
C. Markedly disabled—dormitory.
D. Bedridden or totally confined to wheelchair.
E. Blind.

† Capacity of Infirmary: 30 males and 39 females.

Sources of data

The patients' records, arranged in alphabetical order, were located in the "active files." Every second record was taken from the files and abstracted. A master table was constructed which included the following items: name, sex, age on admission, date of admission, admission diagnosis, cardinal symptom, date of request for medical care, diagnosis, type of treatment, and the results of the treatment. From the completed master table it was possible to construct Tables 20–37, which show the number and type of admission diagnoses and the number and type of requests for medical care by the system affected.

TABLE 20

Admission Diagnoses (Cardio-Respiratory System) Residents of the Home for Aged and Infirm Hebrews, During the Fall of 1953

Admission Diagnosis	Male		Female		
	N.H.*	Non-N.H.†	N.H.	Non-N.H.	Total
1. Arteriosclerotic cardiovascular disease	20	14	35	20	89
2. Bronchial asthma	1	0	1	0	2
3. Bronchiectasis	1	0	0	0	1
4. Chronic bronchitis	2	1	1	0	4
5. Chronic (arrested) pulmonary tuberculosis	0	1	1	2	4
6. Hypertensive cardiovascular disease	6	4	13	8	31
7. Myocardial infarction	2	2	3	2	9
8. Peripheral vascular disease	11	4	13	5	33
9. Pulmonary emphysema	5	3	0	0	8
10. Pernicious anemia	0	1	1	0	2
11. Rheumatic heart disease	1	0	2	0	3
12. Varicose veins	2	4	7	4	17
Total	51	34	77	41	203

* Nursing-Home residents.

† Non-Nursing-Home residents.

TABLE 21

Admission Diagnoses (Endocrine Organs), Residents of the Home for Aged and Infirm Hebrews, During the Fall of 1953

Admission Diagnosis	Male		Female		Total
	N.H.*	Non-N.H.†	N.H.	Non-N.H.	
Diabetes mellitus	3	2	4	5	14
Hyperthyroidism	1	0	4	1	6
Post-thyroidectomy	0	0	1	0	1
Total	4	2	9	6	21

* Nursing-Home residents.

† Non-Nursing-Home residents.

TABLE 22

Admission Diagnoses (Eye, Ear, Nose and Throat), Residents of the Home for Aged and Infirm Hebrews, During the Fall of 1953

Admission Diagnosis	Male		Female		Total
	N.H.*	Non-N.H.†	N.H.	Non-N.H.	
1. Cataracts	0	1	1	2	4
2. Blind (one eye)	1	0	0	0	1
3. Blind (absolute, bilateral)	1	0	1	0	2
4. Chronic glaucoma	0	0	2	1	3
5. Deaf	1	1	7	2	11
6. Melanoma of the iris	0	0	1	0	1
7. Papilloma of the vocal cord	0	1	0	0	1
8. Post-mastoidectomy	0	0	1	1	2
Total	3	3	13	6	25

* Nursing-Home residents.
† Non-Nursing-Home residents.

TABLE 23

Admission Diagnoses (Gastro-intestinal Tract), Residents of the Home for Aged and Infirm Hebrews, During the Fall of 1953

Diagnosis Admission	Male		Female		Total
	N.H.*	Non-N.H.†	N.H.	Non-N.H.	
1. Chronic cholecystitis	0	1	1	3	5
2. Cholelithiasis	1	0	0	2	3
3. Hemorrhoids, and post-hemorrhoidectomy	1	2	1	3	7
4. Hepatomegaly	1	0	1	0	2
5. Inguinal hernia	14	17	1	3	35
6. Other herniae	1	1	1	3	6
7. Peptic ulcer	0	2	0	1	3
8. Post-appendectomy	1	2	1	3	7
9. Post-cholecystectomy	1	0	0	3	4
10. Post-herniorrhaphy	1	3	1	4	9
11. Post-gastrectomy	1	0	0	0	1
Total	22	28	7	25	82

* Nursing-Home residents.
† Non-Nursing Home residents.

Comparative data on admission diagnoses and requests for medical care

Admission diagnoses were compared by sex, and for functional classification. Similar comparisons were made for the requests for medical care. Significance was tested by the chi-square test with d.f. = 1, in all tests (Tables 38–43). The formula employed was chi-square = $\sum[f - f')^2/f')]$.

No data were found with which the requests for medical care could be com-

TABLE 24

Admission Diagnoses (Genito-urinary Tract), Residents of the Home for Aged and Infirm Hebrews, During the Fall of 1953

Admission Diagnosis	Male		Female		Total
	N.H.*	Non-N.H.†	N.H.	Non-N.H.	
1. Bladder stone	0	1	0	0	1
2. Chronic pyelonephritis	1	0	0	0	1
3. Post-carcinoma breast (post-surgery)	0	0	3	1	4
4. Post-prostatectomy	7	6	0	0	13
5. Post-hysterectomy	0	0	6	3	9
6. Post-nephrectomy	1	0	1	0	2
7. Prostatic hypertrophy	6	6	0	0	10
8. Post-salpingo-oophorectomy	0	0	1	3	4
Total	13	13	11	7	44

* Nursing-Home residents.
† Non-Nursing-Home residents.

TABLE 25

Admission Diagnoses (Miscellaneous), Residents of the Home for Aged and Infirm Hebrews, During the Fall of 1953

Admission Diagnosis	Male		Female		Total
	N.H.*	Non-N.H.†	N.H.	Non-N.H.	
1. Obesity	1	3	4	6	14
2. Emaciation	1	0	0	0	1
3. Post-typhoid fever	0	1	0	0	1
4. Post-cholera	0	1	0	0	1
Total	2	5	4	6	17

* Nursing-Home residents.
† Non-Nursing-Home residents.

TABLE 26

Admission Diagnoses (Musculo-Skeletal System), Residents of the Home for Aged and Infirm Hebrews, During the Fall of 1953

Admission Diagnosis	Male		Female		Total
	N.H.*	Non-N.H.†	N.H.	Non-N.H.	
1. Osteoarthritis	3	2	8	6	19
2. Post-amputation (limb)	3	1	1	0	5
3. Post-fracture femur	0	0	2	1	3
4. Spinal fracture	0	0	1	0	1
5. Rheumatoid arthritis	0	0	1	1	2
Total	6	3	13	8	30

* Nursing-Home residents.
† Non-Nursing-Home residents

TABLE 27

Admission Diagnoses (Neuropsychiatric), Residents of the Home for Aged and Infirm Hebrews, During the Fall of 1953

Admission Diagnoses	Male		Female		Total
	N.H.*	Non-N.H.†	N.H.	Non-N.H.	
1. Psychoneuroses, all types	0	0	1	1	2
2. Psychoses, all types	2	2	1	2	7
3. Mental defect	0	0	1	1	2
4. Chronic brain syndrome (non-psychotic)	1	1	2	3	7
5. Parkinsonism	1	0	1	0	2
6. Paralysis of vocal cord	0	1	0	0	1
7. Late latent lues	1	0	2	1	4
8. Residual hemiplegia	0	0	2	0	2
9. Spinal cord tumor (malignant)	0	0	2	0	2
Total	5	4	12	8	29

* Nursing-Home residents.
† Non-Nursing-Home residents.

TABLE 28

Admission Diagnoses (Skin), Residents of the Home for Aged and Infirm Hebrews, During the Fall of 1953

Admission Diagnosis	Male		Female		Total
	N.H.*	Non-N.H.†	N.H.	Non-N.H.	
1. Psoriasis	0	2	0	0	2
2. Epithelioma	0	1	0	0	1
3. Intertrigo	1	0	0	2	3
Total	1	3	0	2	6

* Nursing-Home residents.
† Non-Nursing-Home residents.

pared. However, a comparison was made of the admission diagnoses with the diagnoses of chronic illness observed during a survey of the Eastern District of Baltimore from 1938 to 1943.

Downes and Keller (87) furnished the information concerning the chronic illnesses found during the survey of the Eastern District of Baltimore for the period 1938–1943, the diagnoses of the specific chronic illnesses detected, the number of persons of all ages with each chronic illness, and the percentage of patients with each chronic disease that were age 65 or over. In order to compare the percentage of patients 65 and over in the Baltimore survey with the percentage of such patients having similar diagnoses made on admission to the Home, both the number and the percentage of patients 65 or over with each chronic disease in the Baltimore survey were determined and added to the table (Tables

TABLE 29

Requests for Medical Care (Cardio-Respiratory System), Residents of the Home for Aged and Infirm Hebrews, During the Fall of 1953

Diagnosis	Male		Female		Total
	N.H.*	Non-N.H.†	N.H.	Non-N.H.	
1. Bronchitis, acute	3	5	2	4	14
2. Asthma, bronchial	1	2	1	1	5
3. Acute cardiac failure	7	8	9	11	35
4. Coronary insufficiency	11	9	13	12	45
5. Upper respiratory infection; coryza	14	15	25	33	87
6. Coronary thrombosis	4	6	1	1	12
7. Aneurysm	2	1	0	0	3
8. Hypertensive heart disease	3	2	11	13	29
9. Pneumonia and influenza	40	25	23	20	108
10. Phlebothrombosis; phlebitis; peripheral vascular disease	5	2	6	5	18
11. Polycythemia vera	2	1	2	2	7
12. Pulmonary tuberculosis, chronic	1	3	1	1	6
Total	93	79	94	103	369

* Nursing-Home population.

† Non-Nursing-Home population.

TABLE 30

Requests for Medical Care (Dental), Residents of the Home for Aged and Infirm Hebrews, During the Fall of 1953

Diagnosis	Male		Female		Total
	N.H.*	Non-N.H.†	N.H.	Non-N.H.	
1. Dental caries	0	2	0	3	5
2. Dental abscess	1	3	0	2	6
3. Palatal ulcer	3	5	3	7	18
Total	4	10	3	12	29

* Nursing-Home residents.

† Non-Nursing-Home residents.

TABLE 31

Requests for Medical Care (Endocrine Organs), Residents of the Home for Aged and Infirm Hebrews, During the Fall of 1953

Diagnosis	Male		Female		Total
	N.H.*	Non-N.H.†	N.H.	Non-N.H.	
1. Insulin reaction	0	2	1	2	5
2. Gout	0	1	0	0	1
3. Pre-diabetic coma	1	2	3	3	9
Total	1	5	4	5	15

* Nursing-Home residents.

† Non-Nursing-Home residents.

TABLE 32

Requests for Medical Care (Eye, Ear, Nose and Throat), Residents of the Home for Aged and Infirm Hebrews, During the Fall of 1953

Diagnosis	Male		Female		Total
	N.H.*	Non-N.H.†	N.H.	Non-N.H.	
1. Blepharo-conjunctivitis	21	26	30	57	134
2. Cataracts	5	3	7	11	26
3. Chalazion	1	3	2	6	12
4. Dacryocystitis	1	1	3	3	8
5. Eczema of external ear	0	2	1	0	3
6. Exotropia	0	1	2	0	3
7. Foreign bodies in eye	0	2	2	6	10
8. Glaucoma	0	0	3	3	6
9. Laryngitis	1	2	2	4	9
10. Pharyngitis	1	2	3	4	10
11. Retinitis, diabetic and hypertensive	11	6	15	6	38
12. Otitis media	1	2	3	6	12
13. Tonsillitis	1	3	3	8	15
14. Sinusitis	2	4	5	6	17
Total	45	57	81	120	303

* Nursing-Home residents.
† Non-Nursing-Home residents.

TABLE 33

Requests for Medical Care (Gastro-intestinal Tract), Residents of the Home for Aged and Infirm Hebrews, During the Fall of 1953

Diagnosis	Male		Female		Total
	N.H.*	Non-N.H.†	N.H.	Non-N.H.	
1. Appendicitis, acute	1	2	1	7	11
2. Carcinoma of the bowel	1	1	0	1	3
3. Carcinoma of the stomach	2	0	0	0	2
4. Cholecystitis and cholelithiasis	5	4	7	13	29
5. Chronic cholelithiasis	3	1	2	4	10
6. Gastro-enteritis	11	8	14	26	59
7. Diverticulitis	3	2	2	1	8
8. Hemorrhoids	0	1	1	3	5
9. Hepatitis, viral	1	0	0	0	1
10. Incarceration of a hernia	3	8	2	6	19
11. Peptic ulcer	1	1	0	2	4
12. Esophageal varices	1	0	0	0	1
13. Overdose of a cathartic	1	2	0	3	6
Total	33	30	29	66	153

* Nursing-Home residents.
† Non-Nursing-Home residents.

TABLE 34

Requests for Medical Care (Genito-urinary Tract), Residents of the Home for Aged and Infirm Hebrews, During the Fall of 1953

Diagnosis	Male		Female		Total
	N.H.*	Non-N.H.†	N.H.	Non-N.H.	
1. Carcinoma of the breast	0	0	2	1	3
2. Cystitis, acute	2	1	7	3	13
3. Cystocele-rectocele	0	0	2	2	4
4. Epididymitis	1	1	0	0	2
5. Prostatic hypertrophy	3	5	0	0	8
6. Pyelonephritis, acute	2	1	3	2	8
7. Renal colic	2	0	0	1	3
8. Postoperative; urethral stricture	0	0	1	0	1
Total	10	8	15	9	42

* Nursing-Home residents.
† Non-Nursing-Home residents.

TABLE 35

Requests for Medical Care (Musculo-skeletal System), Residents of the Home for Aged and Infirm Hebrews, During the Fall of 1953

Diagnosis	Male		Female		Total
	N.H.*	Non-N.H.†	N.H.	Non-N.H.	
1. Bursitis	0	0	1	3	5
2. Fibrositis	1	1	6	7	15
3. Fractures	1	3	4	12	20
4. Osteoarthritis	1	2	5	3	11
5. Rheumatoid arthritis	0	0	3	2	5
Total	3	7	19	27	56

* Nursing-Home residents.
† Non-Nursing-Home residents.

TABLE 36

Requests for Medical Care (Neuropsychiatric), Residents of the Home for Aged and Infirm Hebrews, During the Fall of 1953

Diagnoses	Male		Female		Total
	N.H.*	Non-N.H.†	N.H.	Non-N.H.	
1. Psychoneuroses, all types	2	2	4	7	15
2. Psychoses, all types	3	3	3	4	13
3. Chronic brain syndromes (non-psychotic)	4	1	3	4	12
4. Intracranial lesions of vascular origin; also residual manifestations	7	3	8	6	24
5. Neuritis, radiculitis	2	2	3	5	12
6. Parkinsonism	2	0	1	1	4
Total	20	11	22	27	80

* Nursing-Home residents.
† Non-Nursing-Home residents.

TABLE 37

Requests for Medical Care (Skin), Residents of the Home for Aged and Infirm Hebrews, During the Fall of 1953

Diagnoses	Male		Female		Total
	N.H.*	Non-N.H.†	N.H.	Non-N.H.	
1. Contusions and lacerations	2	3	4	6	15
2. Abscess, cellulitis, paronychia, furunculosis	9	12	12	18	51
3. Herpes zoster	2	1	0	0	3
4. Basal-cell tumor	2	3	1	0	6
5. Epithelioma	2	3	1	2	8
6. Seborrhoeic dermatitis	2	0	1	3	6
7. Psoriasis	0	1	0	2	3
8. Intertrigo	0	1	1	3	5
9. Eczematoid dermatitis	2	1	2	4	9
10. Epidermophytosis of feet	0	0	0	1	1
11. Varicose eczema	0	0	0	2	2
Total	21	25	22	41	109

* Nursing-Home residents.
† Non-Nursing-Home residents.

TABLE 38

Comparison of the Number of Admission Diagnoses by Functional Classification Among 498 Residents of the Home for Aged and Infirm Hebrews (Central House and Apartment Projects), During the Fall of 1953

	f	f'*	$(f-f')^2/f'$
Number of admission diagnoses, nursing-home residents	253	145	80.44
Number of admission diagnoses, non-nursing-home residents	204	312	37.38
Total	457	457	$\chi^2 = 117.82$
			$P < .01$

* Nursing-home residents constituted 31.72 per cent, and non-nursing-home residents, 68.28 per cent of the total population (*see* Table 19).

TABLE 39

Comparison of the Number of Admission Diagnoses by Functional Classification Among 322 Female Residents of the Home for Aged and Infirm Hebrews (Central House and Apartment Projects), During the Fall of 1953

	f	f'*	$(f-f')^2/f'$
Number of admission diagnoses, female nursing-home residents	146	83.16	47.48
Number of admission diagnoses, female non-nursing-home residents	109	171.84	22.98
Total	255	255	$\chi^2 = 70.46$
			$P < .01$

* Female nursing-home residents constituted 32.16 per cent, and female non-nursing-home residents, 67.39 per cent of the total female population (*see* Table 19).

TABLE 40

Comparison of the Number of Admission Diagnoses by Functional Classification Among 178 Male Residents of the Home for Aged and Infirm Hebrews (Central House and Apartment Projects), During the Fall of 1953

	f	f'*	$(f-f')^2/f'$
Number of admission diagnoses, male nursing-home residents	107	60.8	35.10
Number of admission diagnoses, male non-nursing-home residents	95	141.2	15.11
Total	202	202	$\chi^2 = 50.21$
		$P < .01$	

* Male nursing-home residents constituted 30.11 per cent, and male non-nursing-home residents, 69.89 per cent of the total male population (*see* Table 19).

TABLE 41

Comparison of the Number of Requests for Medical Care by Functional Classification Among 498 Residents of the Home for Aged and Infirm Hebrews (Central House and Apartment Projects), During the Fall of 1953

	f	f'*	$(f-f')^2/f'$
Requests for medical care, nursing-home residents	519	368.3	61.663
Requests for medical care, non-nursing-home residents	642	792.7	28.620
Total	1161	1161.0	$\chi^2 = 90.303$
		$P < .01$	

* Nursing-home residents constituted 31.72 per cent, non-nursing-home residents, 68.28 per cent of the total population (*see* Table 19).

TABLE 42

Comparison of the Number of Requests for Medical Care by Functional Classification Among 322 Female Residents of the Home for Aged and Infirm Hebrews (Central House and Apartment Projects), During the Fall of 1953

	f	f'*	$(f-f')^2/f'$
Number of requests for medical care, female nursing-home residents	289	227.94	16.35
Number of requests for medical care, female non-nursing-home residents	410	471.06	7.92
Total	699	699	$\chi^2 = 24.27$
		$\text{Dev}/\sigma = \sqrt{24.27} = 4.92$ $P < .01$	

* Female nursing-home residents constituted 32.61 per cent, and female non-nursing-home residents, 67.39 per cent of the total female population (Cf. Table 19).

TABLE 43

Comparison of the Number of Requests for Medical Care by Functional Classification Among 176 Male Residents of the Home for Aged and Infirm Hebrews (Central House and Apartment Projects), During the Fall of 1953

	f	f'*	$(f - f')\ 2/f'$
Number of requests for medical care, male nursing-home residents	230	139.06	59.47
Number of requests for medical care, male non-nursing-home residents	232	322.94	25.60
Total	462	462	$\chi^2 = 85.07$
		$\text{Dev}/\sigma = \sqrt{85.07} = 9.25$ $P < .01$	

* Male nursing-home residents constituted 30.11 per cent, and male non-nursing-home residents, 69.89 per cent of the total male population (*see* Table 19).

TABLE 44

Age Distribution of Persons in Eastern District of Baltimore with Diagnoses of Chronic Disease

[1] Specific Chronic Disease	[2] Total Number of Persons of All Ages	[3] Per Cent in Age Group 65+
Arthritis	267	21.3
Heart disease	278	34.6
Hypertensive heart disease; arteriosclerotic heart disease	160	29.5
Psychoneurosis	113	2.8
Rheumatic fever	103	3.1
Varicose veins	65	14.3
Gall bladder disease	55	9.3
Diabetes mellitus	49	25.6
Mental deficiency	39	0.0
Psychosis	42	4.1
Tuberculosis	51	13.2
Syphilis	36	2.9
Malignant neoplasms	48	39.0
Peptic ulcer	26	0.0
Toxic goiter	11	9.1
Other chronic diseases	137	16.4
Total	1480	

From Downes, J., and Keller, M.: The risk of disability for persons with chronic disease, *Millbank Memorial Fund Quarterly*, **30:** 311 (Oct.) 1952. Table I. Age Distribution of Persons with Specific Chronic Conditions, Eastern District of Baltimore, June, 1938–May, 1943.

TABLE 45

Number of Persons Age 65 and Over and Per Cent of Persons 65 and Over with Chronic Illnesses in Eastern District of Baltimore

[1] Specific Chronic Condition	[2] Number of Persons 65+	[3] Per Cent of Persons 65+ with the Chronic Disease
Arthritis	57	20.0
All cardiovascular disease	143	50.2
(278) (34.6) = 96		
(160) (29.5) = 47		
Mental disease—all categories	5	1.8
(113) (2.8) = 3.0		
(39) (0.0) = 0.0		
(42) (4.1) = 2.0		
Diabetes mellitus	13	4.6
Tuberculosis	7	2.5
Varicose veins	9	3.2
Gall bladder disease	5	1.8
Malignant neoplasms	19	6.7
Rheumatic fever	3	1.1
Syphilis	1	0.4
Peptic ulcer	0	0.0
Toxic goiter	1	0.4
Other chronic disease	22	7.3
Total	285	100.0

From Downes, J., and Keller, M.: The risk of disability for persons with chronic disease, *Millbank Memorial Fund Quarterly*, **30:** 311 (Oct.) 1952. Table I. Age Distribution of Persons with Specific Chronic Conditions, Eastern District of Baltimore, June, 1938-May, 1943.

TABLE 46

Illustration of the Method of Comparing Arthritis as an Example of the Admission Diagnoses, Residents of the Home for Aged and Infirm Hebrews (Central House and Apartment Projects), Fall of 1953, with Diagnoses of Specific Chronic Conditions in Eastern Health District

	Number of Cases of Arthritis	Number of Diagnoses Other Than That of Arthritis	Total	Rate
Home for Aged and Infirm Hebrews (both sexes)	21	436	457	4.6
Eastern Health District	57	228	285	20.0
Total	78	664	742	10.5

$$S.E._{diff.} = \sqrt{\frac{(89.5) \times (10.5)}{457} + \frac{(89.5) \times (10.5)}{285}} = \sqrt{5.36} = 2.32.$$

$$Dev/\sigma = \frac{15.40}{2.32} = 6.64.$$

TABLE 47

Example of the Comparison of Admission Diagnoses, Residents of Home for Aged and Infirm Hebrews During the Survey Period, with Rate Noted by Downes and Keller (87) in Eastern Health District of Baltimore Survey. Example: Cardiovascular Disease

Rate for admission diagnoses—both sexes = 40.0 per cent
Rate in Eastern Health District = 50.2 per cent

	Number with All Diagnoses of Cardiovascular Disease	Number with All Other Diagnoses	Total	Rate
Home for Aged and Infirm Hebrews (both sexes)	182	275	457	40.0
Eastern Health District	143	142	285	50.2
Total	325	417	742	43.8

$$\text{S.E.}_{\text{diff.}} = \sqrt{\frac{(43.8) \times (56.20)}{457} - \frac{(43.8) \times (56.20)}{285}} = \sqrt{14.03} = 3.75.$$

$$\text{Dev}/\sigma = \frac{50.2 - 40.1}{3.75} = 2.69.$$

44 and 45). The diseases compared are recorded later in Part V of this study (Table 145).

Comparison of the differences in the rates was made by determining the standard error of the difference and calculating the relative deviate (Tables 46 and 47).

Prevalence of coronary disease, hypertension and diabetes in the Home, and comparison with data in published reports

The prevalence of a specified disease at a given time is defined as:

$$\frac{\text{all cases of the specific disease at a given time}}{\text{population at a given time}} \times 1000.$$

The number of existing active cases of each chronic disease, on July 1, 1952 was obtained from the "disease index file" of the Medical Department of the Home, in which a continuous listing, using standard nomenclature, of the major chronic diseases met with at the Home is maintained. Therefore, if there were N active cases of a chronic disease on July 1, 1952, and the population, P, was the population present in the Home on July 1, 1952, then $N/P \times 1000$ equalled the prevalence rate for the chronic disease.[3]

It was not possible to compare the prevalence rates for coronary disease with published data since the available data (88) grouped all conditions into one broad category of "heart disease.""Thus in the data resulting from the National Health Survey, it would not be expected that the family informant would

[3] New cases occurring later than July 1, 1952 were not included, since they represented incidence, not prevalence.

be able to report whether the heart condition was arteriosclerotic, hypertensive, congenital, syphilitic, or thyrotoxic, nor to be able to report whether the manifestation was endocarditis, myocarditis, pericarditis, *coronary disease*, or some other category." However, internal comparison was made of the differences in

TABLE 48

Comparison of the Prevalence of Coronary Disease by Sex Among Residents of the Home for Aged and Infirm Hebrews (Central House and Apartment Projects), July 1, 1952

Sex	Number With Coronary Disease	Number Without Coronary Disease	Total	Prevalence Rate per 1,000
Male	24	306	330	72.7
Female	12	571	583	20.6
Total	36	877	913	39.4

$$\text{S.E.}_{\text{diff.}} = \sqrt{\frac{(960.6) \times (39.4)}{330} + \frac{(960.6) \times (39.4)}{583}} = 13.4.$$

$\text{Dev}/\sigma = 52.1/13.4 = 3.89.$

$P < .01.$

TABLE 49

Comparison of the Prevalence of Diabetes by Sex Among Residents of the Home for Aged and Infirm Hebrews (Central House and Apartment Projects), July 1, 1952

Sex	Number with Diabetes	Number Without Diabetes	Total	Proportionate Prevalence Rate per 1,000
Male	6	324	330	18.2
Female	10	573	583	17.2
Total	16	897	913	17.5

$$\text{S.E.}_{\text{diff.}} = \sqrt{\frac{(982.5) \times (17.5)}{330} + \frac{(982.5) \times (17.5)}{583}} = 9.04.$$

$\text{Dev}/\sigma = 1.0/9.04 = 0.11.$

$P < .05.$

TABLE 50

Comparison of Prevalence of Diabetes Noted by Wilkerson and Krall (89) in Oxford, Mass. with the Prevalence in the Home for Aged and Infirm Hebrews (Central House and Apartment Projects), July 1, 1952

	Cases of Diabetes	Cases with Diagnoses Other Than Diabetes	Total	Prevalence Rate per 1000
Oxford	87	4,896	4,983	17.00
Home	16	897	913	17.50
Total	103	5,809	5,896	17.46

$$\text{S.E.}_{\text{diff.}} = \sqrt{\frac{982.54 \times 17.46}{4983} + \frac{982.54 \times 17.46}{913}} = 4.76.$$

$$\text{Dev}/\sigma = \frac{0.50}{4.76} = 0.11.$$

$P > 0.05.$

TABLE 51

Comparison of the Prevalence of Hypertension by Sex Among Residents of the Home for Aged and Infirm Hebrews (Central House, Apartment Projects, and Kingsbridge House) July 1, 1952

Sex	Number with Hypertension	Number Without Hypertension	Total	Prevalence Rate per 1,000
Males	32	298	330	96.9
Females	66	517	583	113.2
Total	98	815	913	107.3

$$\text{S.E.}_{\text{diff.}} = \sqrt{\frac{(892.7) \times (107.3)}{330} + \frac{(892.7) \times (107.3)}{553}} = 21.3.$$

$$\text{Dev}/\sigma = 16.30/21.30 = 0.77.$$

TABLE 52

Comparison of the Prevalence Rate of Hypertension at the Home for Aged and Infirm Hebrews (Central House, Apartment Projects, and Kingsbridge House) with the Prevalence Noted by Collins (88) in the National Health Survey

	f	f'	$(f-f')\,2/f'$
Number with hypertension	98	114.14	2.29
Number with all other diagnoses	815	798.86	0.29
Total	913	913.00	$\chi^2 = 2.58$
	$P > .05$		

TABLE 53

Method of Estimating the Expected Number of Cases of Hypertension in the Home for Aged and Infirm Hebrews on July 1, 1952

Age Group	Population of the Home in Age Group on July 1, 1952	Prevalence Rate per 100,000*	Expected Number of Cases
60–64	20	7379	1.48
65–69	109	9709	10.57
70–74	219	11662	25.62
75–79	256	13403	34.30
80–84	226	13686	20.96
85–	83	13491	11.21
Total	913	$f' = 114.14$	

* From Collins: reference 91.

prevalence rates for coronary disease by sex, by determining the standard error of the difference and calculating the relative deviate (Table 48).

The prevalence rate of diabetes on July 1, 1952 was obtained in a similar fashion, by dividing the number of existing cases of diabetes by the population on July 1, 1952. Internal comparison was also made between the difference in

prevalence rates for male and female diabetics in the same fashion as that described for coronary disease (Table 49).

The diabetes prevalence rate at the Home was compared with the prevalence rate of diabetes reported by Wilkerson and Krall (89). The difference was tested for statistical significance by determining the standard error of the difference and then calculating the relative deviate (Table 50).

In a like fashion the prevalence of hypertension[4] was determined. The rate for both sexes was calculated by dividing the number of existing active cases on July 1, 1952 by the population on July 1, 1952. Comparison was made between the prevalence rate for hypertension for both sexes given by Collins (90) and the prevalence of hypertension for both sexes in the Home. Significance was tested by the chi-square test with d.f. = 1 (Table 51). Internal comparison of the differences in rates between male and female hypertensive subjects was also made by determining the standard error of the difference and calculating the relative deviate (Table 52).

In calculating chi-square, the theoretical value (f') was obtained in the following manner. In Table 4 of his study, Collins gave the age and sex prevalence of hypertension per 100,000. These prevalence rates were applied to the population of the Home on July 1, 1952, and the expected number of hypertensive subjects was obtained, for each age group and for both sexes. The total expected number of hypertensive subjects (f') was the sum of these values (Table 53).

(To be continued)

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90. Collins, S. D.: reference 88, p. 1451.
91. Collins, S. D.: reference 88, Table 4.

[4] Hypertension was measured at the Home by a systolic blood pressure of 160 or more, and diastolic pressure of 90 or more.

LETTER TO THE EDITOR

TREATMENT OF SUPERFICIAL THROMBOPHLEBITIS

To The Editor:

Superficial thrombophlebitis occurring in the legs associated with varicose veins is a chronic condition which does not readily respond to treatment. It often necessitates frequent office visits and sometimes complete bedrest or hospitalization. Many forms of therapy have been advocated, especially the daily intramuscular injections of trypsin in oil, which is the treatment presently in vogue. Patients have worn supporting bandages for months, have had anticoagulant therapy, superficial x-ray therapy to the areas of inflammation, rest in bed, elevation of the legs and applications of heat, and stripping operations on the veins The foregoing procedures have resulted in improvement or cure, but the treatment has been prolonged and the relief of discomfort has not been rapid.

In my use of these forms of therapy I have not been impressed with the rapidity of improvement in symptoms such as pain, tenderness and local muscle spasm.

Recently, in an attempt to limit the pain and muscle spasm which accompanied this condition, I injected small amounts of hydrocortisone acetate suspension (25 mg. per cc.) combined with tetracaine hydrochloride (Pontocaine, 0.15 per cent solution). Each injection contained 0.5 cc. of the hydrocortisone suspension and 1.0 cc. of the tetracaine solution, and was given directly into the painful indurated area of the thrombotic process with a fine needle. The results were very satisfactory. The pain and tenderness improved rapidly, and the next day every patient so treated announced that there had been great improvement. I originally started treatment on many of these patients with daily intramuscular injections of trypsin, rest, elevation and a support bandage; but after starting the use of hydrocortisone in tetracaine locally, the results were immediate and gratifying. I have used this treatment in over 20 cases without any ill effects, and there has been no sloughing of tissue or ulceration. Two injections at intervals of two to three days were sufficient in the great majority of cases; a few patients required three injections. Observations made three months after treatment revealed complete recovery and no relapse in any of the patients treated.

Conclusions: Treatment of superficial thrombophlebitis by the local injection of hydrocortisone suspension combined with tetracaine solution has yielded good results. Pain, swelling, and disability have been greatly improved, and there have been no untoward effects. The response to treatment is rapid, compared to that following other methods, and I have adopted this procedure as the one of choice in the treatment of superficial thrombophlebitis of the legs.

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Abstracts of Current Literature

SERUM CHOLESTEROL, PHOSPHOLIPID AND LIPOPROTEIN LEVELS IN ELDERLY MALE SUBJECTS.

Ackermann, P. G.; Buehler, H. J.; Toro, G., and Kountz, W. B. *Proc. Soc. Exper. Biol. & Med.* **88:** 447 (March) 1955.

The cholesterol, phospholipid, and S_f 12–20 levels in the blood serum were determined in elderly subjects beyond the age of 52 years. In these age groups there was a slight decrease in S_f level with age and a good correlation between the S_f level and the cholesterol level. The phospholipid level was found to vary linearly with the cholesterol level. (Authors' summary.)

NEW THEORIES OF VASCULAR DISEASE WITH SPECIAL REFERENCE TO THE SYNDROME OF POLYCYTHEMIA IN OCULAR PATHOLOGY.

Birge, H. L. *Am. J. Ophth.* **39:** 362 (March) 1955.

Polycythemia may be the cause of vascular complications, especially thromboembolism, in ophthalmologic as well as in other patients. Both vascular accidents following surgery, and those not associated with surgery, often occur in the fifth decade—the age when the polycythemic syndrome becomes most frequent. Polycythemia vera is rare, but the occurrence of relatively polycythemic states is common. The incidence of the polycythemia syndrome varies with social and economic levels, but is highest in males between 50 and 60 years of age, in private practice, and in persons of American, English, and Italian descent. The syndrome occurs in families. Excess blood volume leads to hemorrhage and thrombosis, the latter being twice as frequently the cause of death as the former in polycythemia. When an ophthalmologist sees engorged, cyanotic retinal veins, he should obtain an hematocrit reading. If the value is above 44 in females, or 47 in males, the blood volume should be determined. Case reports illustrate the value of blood volume studies and of the correction of polycythemia in preventing vascular complications. The hematocrit does not always furnish a correct index as to blood volume. The mortality rate was decreased among elderly patients undergoing operation when blood volume studies were performed preoperatively and corrective measures employed. Blood volume studies have been repeatedly valuable in cataract surgery. Recognition and proper treatment of polycythemia in cardiac patients has improved the results of surgery. When polycythemia must be treated quickly, phlebotomy is the procedure of choice. It may also be repeated at intervals in a long-term procedure. The use of radioactive phosphorus is preferred in polycythemia vera. It has the advantage that the red cells formed during treatment are more normal than those remaining after phlebotomy. Phlebotomy yields better results in polycythemia with less danger and more economically than does anticoagulant therapy, which is not favored.

CARDIAC GLYCOSIDES IN THE TREATMENT OF CARDIOGENIC SHOCK.

Gorlin, R., and Robin, E. D. *Brit. M. J.* **1:** 937 (Apr. 16) 1955.

Four patients, one in clinical shock and 3 with shock and pulmonary edema, were treated primarily with a cardiac glycoside intravenously in small doses. All 4 patients showed remarkable clinical response, with a rise in blood pressure, decrease in pulmonary edema and dramatic clearing of coma. Three of the 4 ultimately survived. It is re-emphasized that the shock of myocardial infarction represents true myocardial failure and that the use of digitalis may be highly efficacious. When given, digitalis should be administered in doses fractionally 25 to 50 per cent of the initial dose given to the average cardiac patient. In so doing many of the toxic complications may be avoided. (Authors' conclusions.)

EFFECT OF INTRINSIC FACTOR ON INTESTINAL ABSORPTION OF B_{12} IN AGED PEOPLE.
Jerzy Glass, G. B.; Boyd, L. J.; Goldbloom, A. A., and Rosen, S. Proc. Am. Physiol. Soc., *Federation Proc.* **14:** 57 (March) 1955.

Intestinal absorption of B_{12} was evaluated by measurement of hepatic uptake of Co^{60}-B_{12} in 35 subjects 61 to 90 years old, 15 individuals 28 to 60 years of age, and normal individuals or those with various nonanemic, nondigestive, and nonhepatic disorders. Counts were taken over the liver after the ingestion of this substance and also following the addition of intrinsic-factor concentrate from hog stomach. Gastric acidity was determined in 21 subjects by gastric analysis, urinary resin test, or both, following histamine. Large individual variations were found in the hepatic uptake of radioactivity, indicating variations in the intestinal absorption of B_{12}. Lower uptake values were observed on the average in people between 60 and 80 years of age. Seventeen subjects in all age groups showed improvement in intestinal absorption of B_{12} after the addition of intrinsic-factor concentrate. No more consistent enhancement of absorption after the addition of intrinsic factor occurred in the older age groups than in the younger ones. It cannot yet be ascertained, except in subjects with pernicious anemia or total gastrectomy, in which individuals the intestinal absorption of B_{12} will be benefited by the addition of intrinsic factor. In 6 of 7 individuals 58 to 90 years of age with normal gastric acidity there was no change after the addition of intrinsic factor, whereas an increase in absorption occurred after its addition in 7 of 8 subjects above 50 years of age with gastric anacidity. A new field of clinical applications for intrinsic-factor concentrates appears to be forthcoming.

FLORID PAPILLOMATOSIS OF THE NIPPLE DUCTS.
Jones, D. B. *Cancer* **8:** 315 (Mar.–Apr.) 1955.

Florid papillomatosis of the nipple ducts is an unusual but clean-cut clinical entity. Six cases are presented, one in its preclinical stage. Four of the tumors occurred in elderly women. The lesion is considered to be benign because of its histologic picture—a polymorphous pattern of hyperplasia. The tumor is usually accompanied by nipple discharge and by erosion, erythema, and enlargement of the involved nipple. Ulcers, approximately 0.5 cm. in diameter, may be present in the skin. Microscopically the nipple shows papillary and adenomatous epithelial overgrowth. The histologic picture of the nipple lesions is not specific, inasmuch as similar patterns are seen in subareolar papillary tumors. Clinically, the disease may be mistaken for Paget's disease but can be distinguished microscopically. The heterogeneity of cell type in florid papillomatosis (columnar, polygonal and myoepithelial) and the variation in pattern in various microscopic fields help to distinguish this lesion from papillary carcinoma. The outcome without treatment is unknown. Treatment consists of local excision. Five of the tumors reported were excised and the sixth removed during mastectomy for a supervening breast carcinoma. One patient that could be followed for two years had no recurrence after simple mastectomy. Another followed for three years after a local excision had no recurrence.

LIPOMELANIC RETICULOSIS.
Layman, C. W., and Jackson, R. *A. M. A. Arch. Dermat.* **71:** 303 (March) 1955.

Lipomelanic reticulosis refers to the histologic findings in the enlarged superficial lymph nodes of patients who almost always have generalized erythroderma with varying degrees of exudation, exfoliation, lichenification, pigmentation, excoriation, secondary pyogenic infection, and intense pruritus. Eosinophilia is often found. The lesions in the skin and lymph nodes are reversible. Histologically, the nodes show large, pale, cortical areas with deposits of melanin in their periphery. These areas are composed of reticular cells, the

cytoplasm of which contains cholesterol. There is a polymorphous cell infiltrate. The pathogenesis is unknown. The histologic pattern in the skin is not specific. Six cases are presented, and 2 of giant follicular lymphoblastoma. The latter is a low-grade malignant lymphoma which histologically shows a great increase in the number and size of lymphatic follicles. It frequently is transformed into a more malignant lymphoma. There usually is splenomegaly and involvement of internal nodes. Lipomelanic reticulosis is concluded to be an unusual, chronic lymphadenitis secondary to an erythroderma, and readily distinguished from giant follicular lymphoblastoma. It does not predispose to malignant lymphoma but may occur along with it.

THE POSSIBLE THERAPEUTIC VALUE OF CHOLECYSTECTOMY IN ADAMS-STOKES DISEASE.

McLemore, G. A., Jr., and Levine, S. A. *Am. J. M. Sc.* **229:** 386 (Apr.) 1955.

Six patients with Adams-Stokes syndrome and 1 patient with complete heart block without syncopal attacks underwent cholecystectomy for gallstones. There was no operative mortality, although 3 had attacks of asystole during anesthesia. In each case, the incidence of attacks of syncope was decidedly decreased during the postoperative follow-up period. In 4 cases, the improvement was striking. It would appear that the removal of a diseased gallbladder may not only relieve the patient of biliary symptoms, but improve the cardiac status in selected cases of complete heart block associated with attacks of Adams-Stokes syncope. (From authors' summary.)

STUDIES IN CEREBROVASCULAR DISEASE. III. THE USE OF ANTICOAGULANT DRUGS IN THE TREATMENT OF INSUFFICIENCY OR THROMBOSIS WITHIN THE BASILAR ARTERIAL SYSTEM.

Millikan, C. H.; Siekert, R. G., and Schick, R. M. *Proc. Staff Meet., Mayo Clin.* **30:** 116 (March 23) 1955.

This is the first report of the use of anticoagulant drugs in the treatment of a group of patients suffering from a specific variety of intracranial vascular disease. Such drugs were administered to 5 patients suffering from intermittent insufficiency of the basilar arterial system and to 21 patients suffering from thrombosis within the basilar arterial system. During treatment, in all instances, the attacks suffered by the 5 patients in the first group ceased. Three patients of the second group died—a mortality rate of 14 per cent for this group. The mortality rate for a group of untreated patients was 43 per cent. The length of time anticoagulant drugs should be administered is not known. It is emphasized that the general danger of anticoagulant therapy was carefully assessed in each instance and the use of such treatment *sharply limited* to specific categories of intracranial vascular disease. It is hoped that other workers will investigate the use of anticoagulant drugs in the treatment of insufficiency or thrombosis within the basilar arterial system. It is our impression that such treatment is indicated as soon as a diagnosis of this type of intracranial vascular disease can be established. (From authors' summary.)

CORONARY ARTERY INSUFFICIENCY. A CLINICAL, PHYSIOLOGIC, PATHOLOGIC, AND FUNCTIONAL CONCEPT.

Rakov, H. L. *New York J. Med.* **55:** 644 (March) 1955.

The syndromes of coronary artery insufficiency require qualification as to the pathologic physiology of the coronary circulation and resultant specific myocardial alteration, in order to eliminate confusion in the indiscriminate use of the term. A schematic classification of the types of coronary artery insufficiency on this basis is presented, as follows: *potential*—coronary artery disease unaccompanied by ischemic phenomena; *provisional*—coronary artery disease with ischemic symptoms and alterations prevented by provisional collateral circulation; *acute paroxysmal*—coronary artery disease with transient, relative

insufficiency of the coronary circulation and variable focal myocardial lesions; *acute prolonged nonocclusive*—minimal or moderate coronary artery disease with extrinsically provoked, prolonged, relative coronary insufficiency and myocardial ischemic necrosis, largely subendocardial; *acute prolonged occlusive*—coronary artery disease with acute occlusive lesions and massive ischemic myocardial necrosis; *permanent*—marked coronary artery disease with multiple old occlusions and extensive myocardial fibrosis. Each is described and discussed with citations from the literature. The most reliable diagnostic aid to determining functional recovery following prolonged coronary insufficiency with acute myocardial infarction is the patient's response to activity. Regardless of the statistical prognosis, a diseased, compromised coronary circulation with potential ischemic myocardial alterations exists. The difference in outcome between symptomless individuals and those with clinically evident coronary disease seems to lie not so much in the degree of atherosclerosis present but in the exposure to such adverse influences as sustained effort or emotional strain, which may precipitate prolonged insufficiency or occlusion with infarction. The best guide to rehabilitation is the patient's ability to return to work. The electrocardiogram has proved disappointing in prognosis. Among 200 patients with acute myocardial infarction who survived (two months) the initial episode, the average age at onset was 56 years, the average survival rate 4.1 years (range, three months to eighteen years), and the total deaths 36 per cent. If complete functional recovery is taken to mean return to former occupation without symptoms, 26.5 per cent could be so classified; 17.5 per cent returned to work with symptoms; 33.5 per cent performed work with restricted physical activity; and 22.5 per cent were unable to work. Overenthusiasm about complete recovery is not warranted. Obvious physical incapacity, fear of another attack, the character of the work, the attitude of industry in suitable location, the desire to return to work, the emotional stability, domestic cooperation, and the attitude of the physician all play a role in rehabilitation. The patient should be informed of his condition, so that insofar as possible he can prevent further attacks. He should be given confidence and encouragement. Often the return to work is based upon a philosophy of life rather than upon a medical evaluation and some patients so employed do well despite the unpropitious signs and symptoms.

THE SYSTEMICO-ORAL INTERDEPENDENCY IN CHRONIC DISEASE.

Rockoff, H. S.; Rockoff, S. C., and Sackler, A. M. *Oral Surg.* **8:** 246 (March) 1955.

Chronic systemic diseases related to dentistry are divided into five categories: 1) those producing oral symptoms and lesions (hyperparathyroidism, polycythemia vera), 2) those producing abnormalities in oral structure and function (muscular dystrophy, hypopituitarism, hyperpituitarism), 3) those aggravating established oral defects by lowering resistance (diabetes, acute necrotizing ulcerative gingivitis in myeloblastic leukemia due to the infiltration of mature and immature blood cells into the submucosa with enlargement of the marginal gingivae and infection with Vincent organisms), 4) those altering both the course and prognosis of dental treatment (rheumatic heart disease, Parkinson's disease, Little's disease), and 5) those in which an oral reaction occurs as a result of medical therapy (avitaminosis from a rice diet used in rhemuatic heart disease, Dilantin gingival enlargements in epilepsy). A case report illustrates this relation in each instance. In hyperparathyroidism, failure to eliminate a parathyroid tumor and to restore normal calcium and phosphorus metabolism may result in the loss of teeth. Extractions must be performed with care; the stability of dentures is difficult to maintain. The signs of many blood dyscrasias appear first in the oral cavity. Many cases of polycythemia vera develop into leukemia wherein only ameliorative treatment can be performed. In the polycythemia stage, routine dental treatment can be instituted, with precautions to prevent postoperative hemorrhage. Progressive weakening of muscle groups in muscular dystrophy and enlargement of the tongue markedly alter the development of the oral mechanism. Malposition of teeth caused by hypopituitarism may lead to caries, periodontal disturbances, and

problems in restorative dentistry. In the adult, hyperpituitarism results in acromegaly with changes in the facial skeleton including massiveness and protrusion of the mandible. Oral symptoms in diabetes may include acute periodontal abscesses, polypoid proliferations from under the surface of the free gingiva, or acute pericementitis. Antibiotics are required in patients with rheumatic heart disease, to guard against the exacerbation of heart lesions by blood-borne bacteria. Instrumentation is limited to a few teeth in order to reduce this possibility. Precautions are taken to prevent postoperative bleeding which may occur as a result of the anticoagulant action of Dicumarol. Periodontal conditions cannot be eliminated completely in the patient with Parkinson's disease, because of his inability to maintain high standards of oral hygiene. Dental restorations of all kinds become poor risks.

LYMPHOCYTIC AGGREGATES IN AGING ORGANS.

Sommers, S. C. Proc. Am. Soc. Exper. Path., *Federation Proc.* **14:** 420 (March) 1955.

With age, foci of lymphocytes, usually unorganized and without germinal centers, are observed to collect in human hepatic portal areas, the adrenal medulla, kidney cortex, thyroid gland, peribronchial connective tissue, and in various other organs. Such aggregates may be regarded as indicative of chronic inflammation, but the absence of significant numbers of other types of leukocytes, including plasma cells, does not support this conclusion. Degenerative local dissolutions of the basement membranes and ground substances that normally surround parenchymal cells are demonstrable by newer staining technics, adjacent to the groups of lymphocytes. Exposure of parenchymal-cell proteins and their breakdown products to the internal environment without intervening ground substance is suggested as the stimulus attracting lymphocytes. Lack of significant antigenic activity of autologous proteins and their split products is discussed as explaining the absence of accompanying transitional or mature plasma-cell infiltrates.

UTILIZATION OF NUTRIENTS BY ELDERLY WOMEN.

Swanson, P.; Pesek, I.; Angus, R.; Liu, R., and Schoenleber, F. Proc. Am. Inst. Nutrition, *Federation Proc.* **14:** 452 (March) 1955.

Day-to-day utilization of the nitrogen, calcium and phosphorus provided by self-selected diets was studied in 6 women ranging in age from 52 to 78 years. Metabolism periods varied from thirty to one hundred and fifty days. Taking the first day of the metabolism period as the point of reference, the day-to-day cumulated balances showed that retention of a nutrient is cyclic when the diet contains fair to generous amounts. Thus, even on a good diet an individual may be in negative balance continuously over a period of time, but eventually a shift will occur and the losses accrued will be offset by retentions. As a result, the net balance will be close to equilibrium. Sooner or later, however, the individual will revert to negative balance again and the cycle will be repeated. Situations under which the phenomenon of cyclic retention may not occur are described. Requirements for the nutrients are evaluated and changes in requirements with advancing age indicated. Results obtained in long-term metabolism studies are discussed in relation to those obtained in short periods of observation.

VITAMIN B_{12} LIVER CONTENT IN OLD AGE.

Swendseid, M. E.; Hvolboll, E. E.; Lewis, P. M., and Halsted, J. A. Proc. Am. Physiol. Soc., *Federation Proc.* **14:** 291 (March) 1955.

Liver tissue was obtained at necropsy from individuals 65 to 90 years of age who had had no debilitating disease, and analyzed for vitamin B_{12} using a microbiologic assay. In 25 cases, the values ranged from 0.54 to 1.40 γ of vitamin B_{12} per gram. These values were not significantly different from those obtained when liver tissue from individuals in younger age groups was analyzed. However, values as low as 0.22 γ per gram were found in cases

of neoplastic disease. In untreated pernicious anemia, liver tissue removed for biopsy contained less than 0.10 γ per gram. These results are discussed in relation to availability of vitamin B_{12} liver stores and the nutritional status of this vitamin in old age.

SARCOMA AND SARCOMA-LIKE PROLIFERATIONS OF THE ENDOMETRIAL STROMA. II. CARCINOSARCOMA.

Symmonds, R. E., and Docherty, J. B. *Surg., Gynec. & Obst.* **100:** 322 (March) 1955.

Malignant uterine tumors containing tissues with the characteristics of both carcinoma and sarcoma have been found. Nine tumors under investigation showed an intimate mixture of the two elements, identical histologically to those associated with mesodermal mixed tumors except for the absence of heterotopic elements. Tumors in this group are believed to arise from pleuripotential mesodermal elements which, during malignant transformation, are able to form a variety of tissue types. No histologic criteria could be established for differentiating these tumors as to origin from collision of two separate tumors, combination, or composition. The history, signs, and symptoms associated with carcinosarcoma are similar to those associated with other neoplasms of the uterus. A roentgen-induced menopause had taken place in 5 of the patients. Treatment consists of total hysterectomy and bilateral salpingo-oophorectomy. No definite value could be assigned in this small series to irradiation preoperatively, postoperatively, or for palliation. The prognosis in carcinosarcoma compares with that in uterine sarcoma rather than that associated with endometrial carcinoma. Survival is largely dependent upon the extent of the tumor.

THE TREATMENT OF ANGINA PECTORIS BY INTERNAL MAMMARY ARTERY IMPLANTATION SUPPLEMENTED BY PERICARDIAL FAT WRAP.

Vineburg, A. *Connecticut State M. J.* **19:** 281 (Apr.) 1955.

In experimental animals an implanted internal mammary artery has been shown to send out large branches in the ventricular myocardium in 71 per cent of cases. The branches are sufficiently large to carry a supply of fresh blood into the heart at a rate as high as 51 cc. per minute. The frequency of mammary-coronary anastomosis in human beings now parallels that demonstrated in animal experiments. The operative procedure in human beings is justified because of the possibility that myocardial destruction through the process of progressive coronary artery sclerosis can be stopped if a new source of blood can be brought to the myocardium before it is destroyed. The revascularization of the myocardium should be attempted as soon as possible. The onset of angina in severe form is a definite indication for making an attempt at revascularization by means of surgery. Evidence of progressive coronary artery insufficiency is an important indication for operation. It should also be encouraged in patients partially or totally disabled after a coronary artery occlusion, but without angina at rest. Individuals with status anginosus who experience angina at rest should not undergo the procedure. Other contraindications are: evidence of left ventricular failure, enlargement of the left ventricle (unless it be due to hypertrophy associated with hypertension), an advanced stage of essential hypertension, and evidence of recent myocardial infarction or of active disease. Quinidine and sodium luminal are given preoperatively. The operation should begin immediately upon the patient's arrival in the operating room lest apprehension predispose to the development of a fresh occlusion. It is not commenced unless the blood pressure can be maintained at the proper level—not less than 20 mm. Hg below average preoperative levels. The technic for the operation and for the pericardial fat graft is described. Postoperatively, the maintenance of blood pressure at a constant level and the maintenance of fluid and electrolyte balance are very important. The patient is not moved for forty-eight hours. Approximately 73 per cent of 28 patients so treated were greatly improved and returned to work. The mortality rate for the group was 14 per cent, and among 23 patients without angina at rest, 4.1 per cent. Sixty per cent of the patients operated on are now free of pain.

NEWS AND NOTICES

AMERICAN GERIATRICS SOCIETY

REPORT OF NATIONAL ADVISORY COMMITTEE ON INDUSTRIAL EMPLOYMENT OF OLDER PEOPLE

Dr. George C. Dowd, Chairman of the National Advisory Committee on Industrial Employment of Older People of the American Geriatrics Society, has prepared a splendid report on the work of the Committee entitled "The Senescent in Industry: Medical Evaluation of His Employability and Maintenance."

Copies of this report may be obtained by writing to Dr. George C. Dowd, 216 Main Street, Worcester, Massachusetts.

APPLICATIONS FOR 1957 RESEARCH AWARDS NOW BEING ACCEPTED BY AMERICAN HEART ASSOCIATION

Applications by research investigators for support of studies in or related to the cardiovascular field are now being accepted by the American Heart Association. The awards would be for the fiscal year beginning July 1, 1957. Application deadline for research fellowships and established investigatorships is *September 15, 1956*. For grants-in-aid, applications must be made by *November 1, 1956*. Awards are made in the following categories:

Established Investigatorships: Awarded for periods of up to five years, subject to annual review, in amounts ranging from $6,000 to $9,000 per annum, to scientists of proven ability who have developed in their careers to the point where they are independent investigators.

Research Fellowships: Awarded to young men and women with doctoral degrees for periods of one to two years to enable them to train as investigators under experienced supervision. Annual stipends range from $3,500 to $5,600.

Grants-in-Aid: Made to experienced investigators in varying amounts up to $10,000 to provide support for specified projects.

The Association also maintains another and unique form of research support, the Career Investigatorship. This is given to a limited number of scientists of unusual capacity and accomplishment to assure them of financial support throughout their productive lives. Career Investigators are selected on the initiative of the Heart Association Research Committee and not from applications.

Funds for the research support program are provided from public contributions made to the annual Heart Fund appeal. At least half of all monies received by the American Heart Association national office are allocated to research.

Further information and application forms are available from the Medical Director, American Heart Association, 44 East 23 Street, New York 10.

AHA ANNUAL MEETING AND SCIENTIFIC SESSIONS
SCHEDULED FOR OCTOBER 26–31, 1956
MUSIC HALL AUDITORIUM. CINCINNATI, OHIO

AMERICAN COLLEGE OF PHYSICIANS

The American College of Physicians held its Thirty-seventh Annual Session at Los Angeles, California, April 16–20, 1956, with a gross registration of over 4,500. Dr. Walter L. Palmer of Chicago was inducted as President.

The *1957* Annual Session will be held at Boston, Massachusetts, April 8–12; and the *1958* Annual Session will be held at Atlantic City, New Jersey, April 28–May 2.

AMERICAN UROLOGICAL ASSOCIATION AWARD

Urology Award. The American Urological Association offers an annual award of $1000 (first prize of $500, second prize $300 and third prize $200) for essays on the result of some clinical or laboratory research in Urology. Competition shall be limited to urologists who have been graduated not more than ten years, and to hospital internes and residents doing research work in Urology.

The first prize essay will appear on the program of the forthcoming meeting of the American Urological Association, to be held at the Hotel William Penn, Pittsburgh, Pennsylvania, May 6–9, 1957.

For full particulars write the Executive Secretary, William P. Didusch, 1120 North Charles Street, Baltimore, Maryland. Essays must be in his hands before *December 1, 1956.*